(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 October 2003 (23.10.2003)

PCT

(10) International Publication Number
WO 03/087768 A2

(51) International Patent Classification[7]: G01N

(21) International Application Number: PCT/US03/10870

(22) International Filing Date: 4 April 2003 (04.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/372,843	12 April 2002 (12.04.2002)	US
60/389,987	17 June 2002 (17.06.2002)	US
60/412,418	20 September 2002 (20.09.2002)	US

(71) Applicants *(for all designated States except US)*: **MITOKOR** [US/US]; 11494 Sorrento Valley Road, San Diego, CA 92121 (US). **THE BUCK INSTITUTE FOR AGE RESEARCH** [US/US]; 8001 Redwood Boulevard, Novato, CA 94948-0638 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GHOSH, Soumitra, S.** [US/US]; 12334 Pathos Lane, San Diego, CA 92129 (US). **FAHY, Eoin, D.** [US/US]; 7171 Canyon Hill Way, San Diego, CA 92126 (US). **ZHANG, Bing** [CN/US]; 4840-3 Clairemont Mesa Blvd., San Diego, CA 92117 (US). **GIBSON, Bradford, W.** [US/US]; 1324 Peralta Avenue, Berkeley, CA 94702 (US). **TAYLOR, Steven, W.** [AU/US]; 4012 Willamette Avenue, San Diego, CA 92117 (US). **GLENN, Gary, M.** [US/US]; 2007 Countrywood Ct., Encinitas, CA 92024 (US). **WARNOCK, Dale, E.** [US/US]; 4285 Calle Isabelino, San Diego, CA 92130 (US).

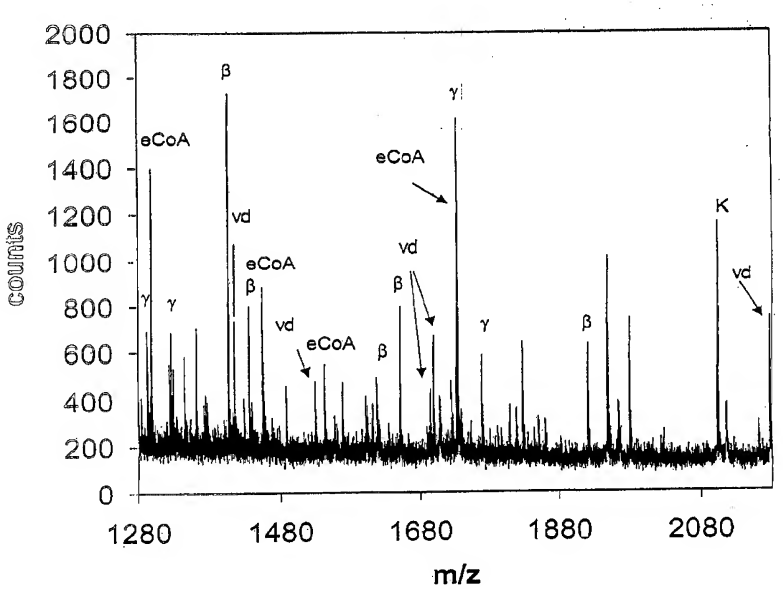
(74) Agents: **ROSENMAN, Stephen, J.** et al.; Seed Intellectual Property Law Group PLLC, Suite 6300, 701 Fifth Avenue, Seattle, WA 98104-7092 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),

[Continued on next page]

(54) Title: TARGETS FOR THERAPEUTIC INTERVENTION IDENTIFIED IN THE MITOCHONDRIAL PROTEOME



(57) Abstract: Mitochondrial targets for drug screening assays and for therapeutic intervention in the treatment of diseases associated with altered mitochondrial function are provided. Complete amino acid sequences [SEQ ID NOS:1-3025] of polypeptides that comprise the human heart mitochondrial proteome are provided, using fractionated proteins derived from highly purified mitochondrial preparations, to identify previously unrecognized mitochondrial molecular components.

WO 03/087768 A2

European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

— *with sequence listing part of description published separately in electronic form and available upon request from the International Bureau*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TARGETS FOR THERAPEUTIC INTERVENTION IDENTIFIED IN THE MITOCHONDRIAL PROTEOME

CROSS-REFERENCES TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Applications Nos. 60/412,418, filed September 20, 2002; 60/389,987, filed June 17, 2002; and 60/372,843, filed April 12, 2002.

STATEMENT REGARDING SEQUENCE LISTING

The Sequence Listing associated with this application is provided on CD-ROM in lieu of a paper copy under AI § 801(a), and is hereby incorporated by reference into the specification. Four CD-ROMs are provided containing identical copies of the sequence listing: CD-ROM No. 1 is labeled "COPY 1 – SEQUENCE LISTING PART," contains the file 465pc.app.txt which is 14.4 MB and created on 4 April 2003; CD-ROM No.2 is labeled "COPY 2 – SEQUENCE LISTING PART," contains the file 465pc.app.txt which is 14.4 MB and created on 4 April 2003; CD-ROM No. 3 is labeled "COPY 3 – SEQUENCE LISTING PART," contains the file 465pc.app.txt which is 14.4 MB and created on 4 April 2003; CD-ROM No. 4 is labeled "CRF," contains the file 465pc.app.txt which is 14.4 MB and created on 4 April 2003.

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates generally to compositions and methods for identifying mitochondrial proteins that are useful as targets for therapeutic intervention in treating diseases associated with altered mitochondrial function. More specifically, the invention is directed to proteomic profiling of proteins and polypeptides of mitochondria and to uses of mitochondrial polypeptides in screening assays for, and as targets of, therapeutic agents.

Description of the Related Art

Mitochondria are the complex subcellular organelles that manufacture bioenergetically essential adenosine triphosphate (ATP) by oxidative phosphorylation, and that promote direct and indirect biochemical regulation of a wide array of cellular respiratory, oxidative and metabolic processes, including aerobic respiration and intracellular calcium regulation. For example, mitochondria provide the subcellular site for physiologically important processes such as the Krebs cycle, the urea cycle, fatty acid β-oxidation, and heme synthesis. Mitochondria also participate in mechanisms of apoptosis, or programmed cell death (*e.g.,* Newmeyer et al., *Cell 79*:353-364, 1994; Liu et al., *Cell 86*:147-157, 1996), which is apparently required for, *inter alia*, normal development of the nervous system and proper functioning of the immune system.

Functional mitochondria contain gene products encoded by mitochondrial genes situated in mitochondrial DNA (mtDNA) and by extramitochondrial (*e.g.,* nuclear) genes not situated in the circular mitochondrial genome. While it has been estimated that a functional human mitochondrion contains on the order of 1,000-1,500 distinct proteins (Lopez et al., 2000 *Electrophoresis* 21:3427; Scheffler, I.E., *Mitochondria*, 1999 Wiley-Liss, Inc., New York; Rabilloud et al., 1998 *Electrophoresis* 19:1006; Scheffler et al., 2001 *Mitochondrion* 1:161; Schatz, G., 1995 *Biochem. Biophys. Acta Mol. Basis Dis.* 1271:123), the 16.5 kb mtDNA encodes 22 tRNAs, two ribosomal RNAs (12s and 16s rRNA) and only 13 polypeptides, which are enzymes of the electron transport chain (ETC), the elaborate multi-subunit complex mitochondrial assembly where, for example, respiratory oxidative phosphorylation takes place. (See, *e.g.,* Wallace et al., in *Mitochondria & Free Radicals in Neurodegenerative Diseases*, M.F. Beal, N. Howell and I. Bodis-Wollner, eds., 1997 Wiley-Liss, Inc., New York, pp. 283-307, and references cited therein; see also, *e.g.,* Scheffler, I.E., *Mitochondria*, 1999 Wiley-Liss, Inc., New York.) Mitochondrial DNA thus includes gene sequences encoding seven subunits of NADH dehydrogenase, also known as ETC Complex I (ND1, ND2, ND3, ND4, ND4L, ND5 and ND6); one subunit of ETC Complex III (ubiquinol: cytochrome c oxidoreductase, Cytb); three cytochrome c

oxidase (ETC Complex IV) subunits (COX1, COX2 and COX3); and two proton-translocating ATP synthase (Complex V) subunits (ATPase6 and ATPase8). All other mitochondrial constituent polypeptides are presumed to be encoded by genes of the extramitochondrial genome, and the number and identities of a large number of these polypeptides remain unknown. Accordingly, for most of the estimated 25,000-40,000 proteins encoded by the human nuclear genome (Venter et al., 2001 *Science* 291:1304; Lander et al., 2001 *Nature* 409:860) little is known regarding subcellular localization, for example, which proteins may be molecular components of mitochondria.

Mitochondria contain an outer mitochondrial membrane that serves as an interface between the organelle and the cytosol, a highly folded inner mitochondrial membrane that appears to form attachments to the outer membrane at multiple sites, and an intermembrane space between the two mitochondrial membranes. The subcompartment within the inner mitochondrial membrane is commonly referred to as the mitochondrial matrix (for review, *see, e.g.,* Ernster et al., 1981 *J. Cell Biol. 91*:227s.) The cristae, originally postulated to occur as infoldings of the inner mitochondrial membrane, have recently been characterized using three-dimensional electron tomography as also including tube-like conduits that may form networks, and that can be connected to the inner membrane by open, circular (30 nm diameter) junctions (Perkins et al., 1997, *Jl. of Struct. Biol. 119*:260). While the outer membrane is freely permeable to ionic and non-ionic solutes having molecular weights less than about ten kilodaltons, the inner mitochondrial membrane exhibits selective and regulated permeability for many small molecules, including certain cations, and is impermeable to large (greater than about 10 kD) molecules.

Four of the five multisubunit protein complexes (Complexes I, III, IV and V) that mediate ETC activity are localized to the inner mitochondrial membrane. The remaining ETC complex (Complex II) is situated in the matrix. In at least three distinct chemical reactions known to take place within the ETC, protons are moved from the mitochondrial matrix, across the inner membrane, to the intermembrane space. This disequilibrium of charged species creates an

electrochemical membrane potential of approximately 220 mV referred to as the "protonmotive force" (PMF). The PMF, which is often represented by the notation Δp, corresponds to the sum of the electric potential ($\Delta\Psi m$) and the pH differential (ΔpH) across the inner membrane according to the equation

$$\Delta p = \Delta\Psi m - Z\Delta pH$$

wherein Z stands for -2.303 RT/F. The value of Z is -59 at 25°C when Δp and $\Delta\Psi m$ are expressed in mV and ΔpH is expressed in pH units (*see, e.g.,* Ernster et al., *J. Cell Biol. 91*:227s, 1981 and references cited therein).

$\Delta\Psi m$ provides the energy for phosphorylation of adenosine diphosphate (ADP) to yield ATP by ETC Complex V, a process that is coupled stoichiometrically with transport of a proton into the matrix. $\Delta\Psi m$ is also the driving force for the influx of cytosolic Ca^{2+} into the mitochondrion. Under normal metabolic conditions, the inner membrane is impermeable to proton movement from the intermembrane space into the matrix, leaving ETC Complex V as the sole means whereby protons can return to the matrix. When, however, the integrity of the inner mitochondrial membrane is compromised, as occurs during mitochondrial permeability transition (MPT) that accompanies certain diseases associated with altered mitochondrial function, protons are able to bypass the conduit of Complex V without generating ATP, thereby uncoupling respiration. During MPT, $\Delta\Psi m$ collapses and mitochondrial membranes lose the ability to selectively regulate permeability to solutes both small (*e.g.,* ionic Ca^{2+}, Na^{+}, K^{+} and H^{+}) and large (*e.g.,* proteins).

A number of diseases, disorders or conditions, including degenerative diseases, are thought to be caused by, or are associated with, alterations in mitochondrial function as provided herein. These disorders include Alzheimer's Disease (AD), diabetes mellitus, Parkinson's Disease (PD), Huntington's disease, Freidreich's ataxia, atherosclerosis, hypertension, ischemia-reperfusion injury, osteoarthritis, inflammatory diseases, amyotrophic lateral sclerosis (ALS), Wilson disease, autosomal recessive hereditary spastic paraplegia, Leigh syndrome, benign and fatal infantile myopathies, multiple sclerosis, dystonia, Leber's hereditary optic neuropathy, schizophrenia, cancer;

psoriasis; Down's syndrome, hyperproliferative disorders; mitochondrial diabetes and deafness (MIDD) and myodegenerative disorders such as "mitochondrial encephalopathy, lactic acidosis, and stroke" (MELAS), and "myoclonic epilepsy ragged red fiber syndrome" (MERRF), as well as other mitochondrial respiratory chain diseases (reviewed in Chinnery et al., 1999 *J. Med. Genet.* 36:425; see also references cited therein). Diseases associated with altered mitochondrial function thus include these and other diseases in which one or more levels of an indicator of altered mitochondrial function differ in a statistically significant manner from the corresponding indicator levels found in clinically normal subjects known to be free of a presence or risk of such disease. Other diseases involving altered metabolism or respiration within cells may also be regarded as diseases associated with altered mitochondrial function, for example, those in which free radicals such as reactive oxygen species (ROS) contribute to pathogenesis. Certain diseases associated with altered mitochondrial function appear to involve states of insufficient apoptosis (*e.g.,* cancer and autoimmune diseases) or excessive levels of apoptosis (*e.g.,* stroke and neurodegeneration). For a general review of apoptosis, and the role of mitochondria therein, see, *e.g.,* Green and Reed, *Science 281*:1309-1312, 1998; Green, *Cell 94*:695-698, 1998 and Kromer, *Nature Medicine 3*:614-620, 1997. The extensive list of additional diseases associated with altered mitochondrial function continues to expand as aberrant mitochondrial or mitonuclear activities are implicated in particular disease processes.

For instance, free radical production in biological systems is known to result in the generation of reactive species that can chemically modify molecular components of cells and tissues. Such modifications can alter or disrupt structural and/or functional properties of these molecules, leading to compromised cellular activity and tissue damage. Mitochondria are a primary source of free radicals in biological systems (see, *e.g.,* Murphy et al., 1998 in *Mitochondria and Free Radicals in Neurodegenerative Diseases*, Beal, Howell and Bodis-Wollner, Eds., Wiley-Liss, New York, pp. 159-186 and references cited therein), and altered mitochondrial function, such as failure at any step of the mitochondrial electron

transport chain (ETC), may also lead to the generation of highly reactive free radicals. Thus, free radicals generated in biological systems, including free radicals resulting from altered mitochondrial function or from extramitochondrial sources, include reactive oxygen species (ROS), for example, superoxide, peroxynitrite and hydroxyl radicals, and potentially other reactive species that may be toxic to cells. Diseases associated with altered mitochondrial function therefore include disorders in which free radicals contribute to pathogenesis at the molecular level (see, *e.g.,* Halliwell B. and J.M.C. Gutteridge, *Free Radicals in Biology and Medicine*, 1989 Clarendon Press, Oxford, UK).

A particularly prevalent example of a disease associated with altered mitochondrial function is type 2 diabetes mellitus, or "late onset" diabetes, a common, degenerative disease affecting 5 to 10 percent of the population in developed countries. The propensity for developing type 2 diabetes mellitus ("type 2 DM") is reportedly maternally inherited, suggesting a mitochondrial genetic involvement. (Alcolado, J.C. and Alcolado, R., *Br. Med. J. 302*:1178-1180 (1991); Reny, S.L., *International J. Epidem. 23*:886-890 (1994)). Diabetes is a heterogeneous disorder with a strong genetic component; monozygotic twins are highly concordant and there is a high incidence of the disease among first degree relatives of affected individuals.

At the cellular level, the degenerative phenotype that may be characteristic of late onset diabetes mellitus includes indicators of altered mitochondrial respiratory function, for example impaired insulin secretion, decreased ATP synthesis and increased levels of reactive oxygen species. Studies have shown that type 2 DM may be preceded by or associated with certain related disorders. For example, it is estimated that forty million individuals in the U.S. suffer from impaired glucose tolerance (IGT). Following a glucose load, ciruculating glucose concentrations in IGT patients rise to higher levels, and return to baseline levels more slowly, than in unaffected individuals. A small percentage of IGT individuals (5-10%) progress to non-insulin dependent diabetes (NIDDM) each year. This form of diabetes mellitus, type 2 DM, is associated with decreased release of insulin by pancreatic beta cells and a decreased end-organ response to

insulin. Other symptoms of diabetes mellitus and conditions that precede or are associated with diabetes mellitus include obesity, vascular pathologies, peripheral and sensory neuropathies and blindness.

Despite intense effort, nuclear genes that segregate with diabetes mellitus are rare and include, for example, mutations in the insulin gene, the insulin receptor gene and the glucokinase gene. By comparison, although a number of altered mitochondrial genes that segregate with diabetes mellitus have been reported (*see generally e.g.,* PCT/US95/04063), relationships amongst mitochondrial and extramitochondrial factors that contribute to cellular respiratory and/or metabolic activities as they pertain to diabetes remain poorly understood.

Current pharmacological therapies for type 2 DM include injected insulin, and oral agents that are designed to lower blood glucose levels. Currently available oral agents include (i) the sulfonylureas, which act by enhancing the sensitivity of the pancreatic beta cell to glucose, thereby increasing insulin secretion in response to a given glucose load; (ii) the biguanides, which improve glucose disposal rates and inhibit hepatic glucose output; (iii) the thiazolidinediones, which improve peripheral insulin sensitivity through interaction with nuclear peroxisome proliferator-activated receptors (PPAR, see, *e.g.,* Spiegelman, 1998 *Diabetes* 47:507-514; Schoonjans et al., 1997 *Curr. Opin. Lipidol.* 8:159-166; Staels et al., 1997 *Biochimie* 79:95-99), (iv) repaglinide, which enhances insulin secretion through interaction with ATP-dependent potassium channels; and (v) acarbose, which decreases intestinal absorption of carbohydrates. It is clear that none of the current pharmacological therapies corrects the underlying biochemical defect in type 2 DM. Neither do any of these currently available treatments improve all of the physiological abnormalities in type 2 DM such as impaired insulin secretion, insulin resistance and/or excessive hepatic glucose output. In addition, treatment failures are common with these agents, such that multi-drug therapy is frequently necessary.

Clearly there is a need for improved diagnostic methods for early detection of a risk for developing a disease associated with altered mitochondrial function, and for better therapeutics that are specifically targeted to correct

biochemical and/or metabolic defects responsible for such disease, regardless of whether such a defect underlying altered mitochondrial function may have mitochondrial or extramitochondrial origins. The present invention provides compositions and methods related to identification of mitochondrial targets for therapeutic intervention in treating these diseases, and offers other related advantages.

BRIEF SUMMARY OF THE INVENTION

The present invention provides the identities of 3025 polypeptide sequences [SEQ ID NOS:1-3025] that are constituents of the human mitochondrial proteome. It is therefore an aspect of the present invention to provide a method for identifying a mitochondrial target for therapeutic intervention in treatment of a disease associated with altered mitochondrial function, comprising (a) determining a presence, in a biological sample from a subject known to have or suspected of having a disease associated with altered mitochondrial function, of at least one modified polypeptide, the modified polypeptide comprising at least one modification to a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1- 3025; and (b) correlating the modification with at least one disease associated with altered mitochondrial function, and therefrom identifying a mitochondrial target for therapeutic intervention.

In certain embodiments the modified polypeptide exhibits altered biological activity. In certain embodiments the biological sample is selected from the group consisting of blood, skin, skeletal muscle, liver and cartilage. In certain embodiments the disease associated with altered mitochondrial function is Alzheimer's disease, diabetes mellitus, Parkinson's disease, Huntington's disease, osteoarthritis, dystonia, Leber's hereditary optic neuropathy (LHON), mitochondrial encephalopathy, lactic acidosis, and stroke (MELAS), myoclonic epilepsy ragged red fiber syndrome (MERRF) or cancer. In certain embodiments the modification is an amino acid substitution, an amino acid insertion, an amino acid deletion, a posttranslational modification or an altered expression level, and in certain further embodiments the posttranslational modification is glycosylation, phosphorylation,

nitration, nitrosylation, amidation, fatty acylation or oxidative modification, including, for example, oxidative post-translational modification of tryptophan residues.

In certain other embodiments the present invention provides a method of identifying an agent for treating a disease associated with altered mitochondrial function, comprising (a) contacting a candidate agent with a biological sample from a subject having a disease associated with altered mitochondrial function, wherein the sample comprises at least one polypeptide that exhibits altered biological activity which accompanies the disease and wherein the polypeptide is (i) a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1- 3025, or (ii) a modified polypeptide that comprises at least one modification to a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1- 3025; and (b) determining an increase or decrease in the altered biological activity of the polypeptide in the presence of the candidate agent relative to the level of the altered biological activity in the absence of the candidate agent, and therefrom identifying an agent for treating a disease associated with altered mitochondrial function.

In certain embodiments the altered biological activity is an indicator of altered mitochondrial function that is ATP biosynthesis (*e.g.*, an ATP biosynthesis factor), oxidative phosphorylation, mitochondrial calcium uptake, mitochondrial calcium release, maintenance of inner mitochondrial membrane potential, mitochondrial permeability transition, ETC-mediated electron transport or mitochondrial intermembrane space protein release. In certain other embodiments the sample is a cell, a mitochondria enriched sample, an isolated mitochondrion or a submitochondrial particle. In certain embodiments the disease associated with altered mitochondrial function is Alzheimer's disease, diabetes mellitus, Parkinson's disease, Huntington's disease, osteoarthritis, dystonia, Leber's hereditary optic neuropathy (LHON), mitochondrial encephalopathy, lactic acidosis, and stroke (MELAS), myoclonic epilepsy ragged red fiber syndrome (MERRF) or cancer.

According to certain other embodiments there is provided by the present invention a method of treating a disease associated with altered mitochondrial function comprising administering to a subject in need thereof an agent that compensates for at least one biological activity of a polypeptide that exhibits altered biological activity which accompanies the disease, wherein the polypeptide is (i) a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1-3025, or (ii) a modified polypeptide that comprises at least one modification to a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1-3025. In another embodiment the invention provides a method for identifying a risk for having or a presence of a disease associated with altered mitochondrial function, comprising (a) determining a presence, in a biological sample from a subject suspected of having a disease associated with altered mitochondrial function, of at least one modified polypeptide, the modified polypeptide comprising at least one modification to a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1- 3025, wherein the modification correlates with at least one disease associated with altered mitochondrial function, and therefrom identifying a risk for or presence of disease.

Certain other embodiments of the invention provide a method of identifying an agent for treating a disease associated with altered mitochondrial function, comprising (a) contacting a candidate agent with an isolated polypeptide that exhibits altered biological activity which accompanies a disease associated with altered mitochondrial function, wherein the polypeptide is selected from the group consisting of (i) a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1-3025 and (ii) a modified polypeptide that comprises at least one modification to a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1-3025; and (b) determining an increase or decrease in the altered biological activity of the polypeptide in the presence of the candidate agent relative to the level of the altered biological activity in the absence of the candidate agent, and therefrom identifying an agent for treating a disease associated with altered mitochondrial function. In certain further embodiments the disease associated with altered mitochondrial function is Alzheimer's disease,

diabetes mellitus, Parkinson's disease, Huntington's disease, osteoarthritis, dystonia, Leber's hereditary optic neuropathy (LHON), mitochondrial encephalopathy, lactic acidosis, and stroke (MELAS), myoclonic epilepsy ragged red fiber syndrome (MERRF), or cancer. In other further embodiments the isolated polypeptide is present in a preparation that is a submitochondrial particle, a proteoliposome or a mitochondrial protein fraction.

In another embodiment the invention provides a method of identifying an agent for treating a disease associated with altered mitochondrial function, comprising (a) administering a candidate agent to a subject having a disease associated with altered mitochondrial function; and (b) determining, in a first biological sample obtained from the subject prior to the step of administering the candidate agent and in a second biological sample obtained from the subject subsequent to the step of administering the candidate agent, wherein each of said first and second samples comprises at least one polypeptide that exhibits altered biological activity which accompanies said disease and wherein the polypeptide is selected from the group consisting of (i) a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1-3025 and (ii) a modified polypeptide that comprises at least one modification to a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1-3025, an increase or decrease in the altered biological activity of the polypeptide in the second sample relative to the level of the altered biological activity in the first sample, and therefrom identifying an agent for treating a disease associated with altered mitochondrial function. In a further embodiment, the altered biological activity is an indicator of altered mitochondrial function that is ATP biosynthesis, oxidative phosphorylation, calcium uptake, calcium release, maintenance of inner mitochondrial membrane potential, mitochondrial permeability transition, ETC-mediated electron transport or intermembrane space protein release. In another further embodiment the sample is a cell, a mitochondria enriched sample, an isolated mitochondrion or a submitochondrial particle. In certain other further embodiments, the disease associated with altered mitochondrial function is Alzheimer's disease, diabetes mellitus, Parkinson's disease, Huntington's disease,

osteoarthritis, dystonia, Leber's hereditary optic neuropathy (LHON), mitochondrial encephalopathy, lactic acidosis, and stroke (MELAS), myoclonic epilepsy ragged red fiber syndrome (MERRF), or cancer.

These and other aspects of the present invention will become evident upon reference to the following detailed description and attached drawings. In addition, various references are set forth below which describe in more detail certain procedures or compositions and are therefore incorporated by reference in their entireties.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows representative western immunoblot analysis (Fig. 1A) of indicated mitochondrial ETC proteins in sucrose density gradient fractionated isolated human heart mitochondria, following resolution of proteins by one-dimensional polyacrylamide gel electrophoresis (Fig. 1B).

Figure 2 shows a representative MALDI mass spectrum for a single band excised from a one-dimensional polyacrylamide gel following electrophoretic resolution of proteins from sucrose density gradient fractionated isolated human heart mitochondria. Peptides are from indicated mitochondrial proteins as follows: β = ATP synthase beta subunit, γ = ATP synthase gamma subunit, eCoA = enlyl-CoA hydratase, and vd = voltage dependent anion channel 1 (VDAC-1). (K = keratin.)

Figure 3 shows products of tryptophan oxidation in proteins.

Figure 4 shows MALDI-TOF mass spectrometry of two peptides from complex I subunit NDUFS4 displaying (A) tryptophan and (B) methionine oxidation. The samples were as follows (i) human heart mitochondria complex I (HHM individual #1) prepared by sucrose density gradient fractionation (SDG) and 1D electrophoresis; (ii) HHM individual #1 prepared by immunocapture and 1D electrophoresis (iii) HHM individual #2 prepared by immunocapture and 1D electrophoresis; (iv) HHM individuals #3,4,5 (pooled) prepared by SDG and 1D electrophoresis; (v) bovine heart mitochondria (BHM animal #1) prepared by SDG

and 1D electrophoresis; (vi) (BHM animal #2) prepared by SDG and 2D electrophoresis.

Figure 5 shows a comparison of the distribution of (a) tryptophan and (b) methionine oxidation for complex I subunit peptides.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method for identifying mitochondrial polypeptide targets for therapeutic intervention in the treatment of diseases associated with altered mitochondrial function, and a method for identifying agents for treating such diseases, as well as other related advantages.

The invention derives from characterization of the human heart mitochondrial proteome as described herein, to arrive at the surprising discovery and recognition for the first time that polypeptides having the amino acid sequences set forth in SEQ ID NOS:1-3025 are mitochondrial molecular components. This unexpected determination, that isolated human mitochondria comprise polypeptides having the amino acid sequences set forth in SEQ ID NOS:1-3025, is usefully combined with methods for determining the presence of a disease associated with altered mitochondrial function, and with methods for determining modification to, and altered biological activity of, a polypeptide, to provide targets for drug-screening assays and for therapeutic agents. According to certain embodiments, the invention relates to determination of at least one modified polypeptide that comprises a modification to a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS:1-3025, and according to certain other embodiments the invention relates to determination of a profile comprising a plurality (*e.g.*, two or more) of polypeptides having distinct amino acid sequences wherein at least one such polypeptide has one of the amino sequences set forth in SEQ ID NOS:1-3025, and has not been previously identified as a mitochondrial component.

Thus, it is an aspect of the present invention to provide a method for identifying a mitochondrial target for therapeutic intervention in treatment of a disease associated with altered mitochondrial function, comprising (a) determining

a presence, in a biological sample from a subject known to have or suspected of having a disease associated with altered mitochondrial function, of at least one modified polypeptide, the modified polypeptide comprising at least one modification to a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1- 3025; and (b) correlating the modification with at least one disease associated with altered mitochondrial function, and therefrom identifying a mitochondrial target for therapeutic intervention.

Biological samples may comprise any tissue or cell preparation containing mitochondria. Biological samples may be provided by obtaining a blood sample, biopsy specimen, tissue explant, organ culture or any other tissue or cell preparation from a subject or a biological source. The subject or biological source may be a human or non-human animal, a primary cell culture or culture adapted cell line including but not limited to genetically engineered cell lines that may contain chromosomally integrated or episomal recombinant nucleic acid sequences, immortal, immortalized or immortalizable cell lines (*e.g.,* capable of at least ten cell doublings *in vitro*), somatic cell hybrid or cytoplasmic hybrid "cybrid" cell lines (including mitochondrial cybrid cells having nuclear and mitochondrial DNAs of differing biological origins, see, *e.g.*, U.S. Patent No. 5,888,498 and International Publication No. WO 95/26793), differentiated or differentiatable cell lines, transformed cell lines and the like. In certain preferred embodiments of the invention, the subject or biological source may be suspected of having or being at risk for having a disease associated with altered mitochondrial function, including, for example, altered mitochondrial molecular composition or constitution, or oxidative modification of one or more mitochondrial proteins, and in certain preferred embodiments of the invention the subject or biological source may be known to be free of a risk or presence of such a disease. In certain other preferred embodiments a biological sample comprises a cybrid cell line having nuclear and mitochondrial DNAs of differing biological origins, which in certain embodiments may be a human cell, an immortal cell, a neuronal cell, a neuroblastoma or other transformed cell, for example, a SH-SY5Y human neuroblastoma cell. In certain other particularly preferred embodiments a biological sample comprises a sample

readily obtained from a subject or biological source, such as blood, skin, skeletal muscle, liver or cartilage.

By way of background, mitochondria are comprised of "mitochondrial molecular components", which may be any protein, polypeptide, peptide, amino acid, or derivative thereof; any lipid, fatty acid or the like, or derivative thereof; any carbohydrate, saccharide or the like or derivative thereof, any nucleic acid, nucleotide, nucleoside, purine, pyrimidine or related molecule, or derivative thereof, or the like; or any other biological molecule that is a constituent of a mitochondrion, which may include molecules that are integral or stable components of mitochondrial structure, and may also include molecules that may transiently associate with mitochondria under certain conditions, for example, regulated intracellular events that involve mitochondria. In the most preferred embodiments, the present invention is directed to compositions and methods that relate to those mitochondrial molecular components that are mitochondrial polypeptides or proteins, although the invention need not be so limited.

In certain preferred embodiments of the present invention, a mitochondrial protein fraction is derived from the biological sample as provided herein. A protein fraction may be any preparation that contains at least one protein that is present in the sample and which may be obtained by processing a biological sample according to any biological and/or biochemical methods useful for isolating or otherwise separating a protein from its biological source. Those familiar with the art will be able to select an appropriate method depending on the biological starting material and other factors. Such methods may include, but need not be limited to, cell fractionation, density sedimentation, differential extraction, salt precipitation, ultrafiltration, gel filtration, ion-exchange chromatography, partition chromatography, hydrophobic chromatography, reversed-phase chromatography, one- and two-dimensional electrophoresis, affinity techniques or any other suitable separation method.

It will be noted that in certain particularly preferred embodiments of the present invention, at least one sample as described herein comprises a "mitochondria enriched" sample, which refers to a sample that comprises one or

more mitochondria and that is substantially depleted (*i.e.*, partially or fully depleted, where the degree of depletion of a given component can be quantified to show that its presence has been reduced in a statistically significant manner) of one or more non-mitochondrial marker proteins to the extent such markers can be removed from a preparation and are detectable, as described herein and known to the art. Thus, for example, cell fractionation techniques for the enrichment and detection of mitochondria, and/or biochemical markers characteristic of these and other defined organelles, may be used to determine that a particular subcellular fraction containing one or more detectable organelle-specific or organelle-associated markers or polypeptides, as provided herein, is substantially enriched in mitochondria (see, *e.g.,* Ernster et al., 1981 *J. Cell Biol. 91*:227s; see also, e.g., Rickwood et al., 1987, *Mitochondria, a practical approach* (Darley-Usmar, R., Wilson,, Ed.), IRL Press; Storrie and Madden, 1990 *Methods in Enzymology* 182, 203-225).

For example, and in certain preferred embodiments including methods for determining the presence in a biological sample of a mitochondrial target polypeptide for therapeutic intervention or for screening a candidate agent for its ability to alter the biological activity of such a target, a mitochondrial molecular component such as any protein or polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS:1-3025 may be obtained from a preparation of isolated mitochondria and/or from a preparation of isolated submitochondrial particles (SMP). Techniques for isolating mitochondria and for preparing SMP are well known to the person having ordinary skill in the art and may include certain minor modifications as appropriate for the particular conditions selected *(e.g.,* Smith, A.L., *Meths. Enzymol.* 10:81-86; Darley-Usman et al., (eds.), *Mitochondria: A Practical Approach*, IRL Press, Oxford, UK; Storrie et al., 1990 *Meths. Enzymol.* 182:203-255). Cell or tissue lysates, homogenates, extracts, suspensions, fractions or the like, or other preparations containing partially or fully purified mitochondrial molecular components such as mitochondrial proteins (*e.g.*, MCA) may also be useful in these and related embodiments. According to certain other related embodiments, one or more isolated mitochondrial molecular

components such as isolated targets for therapeutic intervention in the treatment of a disease associated with altered mitochondrial function may be present in membrane vesicles such as uni- or multilamellar membrane vesicles, or reconstituted into naturally derived or synthetic liposomes or proteoliposomes or similar membrane-bounded compartments, or the like, according to generally accepted methodologies (*e.g.*, Jezek et al., 1990 *J. Biol. Chem.* 265:10522-10526).

Affinity techniques are particularly useful in the context of the present invention, and may include any method that exploits a specific binding interaction with a mitochondrial protein or peptide to effect a separation. Other useful affinity techniques include immunological techniques for isolating specific proteins or peptides, which techniques rely on specific binding interaction between antibody combining sites for antigen and antigenic determinants present in the proteins or peptides. Immunological techniques include, but need not be limited to, immunoaffinity chromatography, immunoprecipitation, solid phase immunoadsorption or other immunoaffinity methods. See, for example, Scopes, R.K., *Protein Purification: Principles and Practice*, 1987, Springer-Verlag, NY; Weir, D.M., *Handbook of Experimental Immunology*, 1986, Blackwell Scientific, Boston; Deutscher, M.P., *Guide to Protein Purification*, 1990, *Methods in Enzymology* Vol. 182, Academic Press, New York; and Hermanson, G.T. et al., *Immobilized Affinity Ligand Techniques*, 1992, Academic Press, Inc., California; which are hereby incorporated by reference in their entireties, for details regarding techniques for isolating and characterizing proteins and peptides, including affinity techniques.

The term "isolated" means that the material is removed from its original environment (*e.g.*, the natural environment if it is naturally occurring). For instance, a naturally occurring protein or peptide present in a living animal is not isolated, but the same protein or peptide, separated from some or all of the co-existing materials in the natural system, is isolated. Thus, for example, such proteins could be part of a multisubunit complex or a membrane vesicle, and/or

such peptides could be part of a composition, and still be isolated in that such complex, vesicle or composition is not part of its natural environment.

"Biological activity" of a protein may be any detectable parameter that directly relates to a condition, process, pathway, dynamic structure, state or other activity involving the protein and that permits detection of altered protein function in a biological sample from a subject or biological source, or in a preparation of the protein isolated therefrom. The methods of the present invention thus pertain in part to such correlation where the protein having biological activity may be, for example, an enzyme, a structural protein, a receptor, a ligand, a membrane channel, a regulatory protein, a subunit, a complex component, a chaperone protein, a binding protein or a protein having a biological activity according to other criteria including those provided herein. Such activity may include the amount of a protein that is present, or the amount of a given protein's function that is detectable.

"Altered biological activity" of a protein may refer to any condition or state, including those that accompany a disease associated with altered mitochondrial function, for example, a disease or disorder characterized by altered (*e.g.,* increased or decreased in a statistically significant manner relative to an appropriate control) mitochondrial molecular composition or constitution or by modification of a mitochondrial protein as provided herein (and in particular, *e.g.*, a modification to a polypeptide that in its unmodified form comprises an amino acid sequence as set forth in any one of SEQ ID NOS:1-3025), where any structure or activity that is directly or indirectly related to a particular protein's function (or multiple functions) has been changed in a statistically significant manner relative to a control or standard.

Altered biological activity may have its origin in deletion, substitution or insertion of one or more amino acids in a mitochondrial protein; in posttranslational modification of a mitochondrial protein; in an altered expression level (*e.g.,* a statistically significant increase or decrease in the amount present) of a mitochondrial protein; in oxidatively modified structures or oxidative events as well as in oxidation-independent structures or events, in direct interactions

between mitochondrial and extramitochondrial genes and/or their gene products, or in structural or functional changes that occur as the result of interactions between intermediates that may be formed as the result of such interactions, including metabolites, catabolites, substrates, precursors, cofactors and the like. According to certain embodiments as provided herein, altered biological activity of a protein may also result from direct or indirect interaction of a biologically active protein with an introduced agent such as an agent for treating a disease associated with altered mitochondrial function as described herein, for example, a small molecule.

Additionally, altered biological activity of a mitochondrial protein (including proteins having any amino acid sequence set forth in SEQ ID NOS:1-3025 or modified forms of such proteins as provided herein) may result in altered respiratory, metabolic or other biochemical or biophysical activity in some or all cells of a biological source having a disease associated with altered mitochondrial function. As non-limiting examples, markedly impaired ETC activity may be related to altered biological activity of at least one protein, as may be generation of increased free radicals such as reactive oxygen species (ROS) or defective oxidative phosphorylation. As further examples, altered mitochondrial membrane potential, induction of apoptotic pathways and formation of atypical chemical and biochemical crosslinked species within a cell, whether by enzymatic or non-enzymatic mechanisms, may all be regarded as indicative of altered protein biological activity. Non-limiting examples of altered protein biological activity are described in greater detail below.

Thus, by way of non-limiting examples, coordinated replication of nuclear and mitochondrial DNA (reviewed in Clayton, D.A., 1992, *Int. Rev. Cytol.* 141, 217-232; and Shadel and Clayton, 1997, *Annu. Rev. Biochem.* 66, 409-435), or mitochondrial DNA transcription and RNA processing (Shadel and Clayton, 1996, *Methods Enzymol.* 264, 149-158; Micol et al., 1996, *Methods Enzymol.* 264, 158-173) both incompletely understood processes involving a large number of mitochondrial and extramitochondrial proteins, may be altered mitochondrial functions in certain diseases associated with altered mitochondrial function as

provided herein. According to these examples, the disclosure herein -- that polypeptides such as those listed in Table 2 alongside the functional classifications such as "carrier", "DNA synthesis", "nucleotide metabolism", "transcription" and "transport", are *mitochondrial* components -- provides targets for therapeutic intervention in such diseases. In like manner, the disclosure herein that other polypeptides having amino acid sequences as set forth in SEQ ID NOS:1-3025 are mitochondrial components also identifies these proteins as targets for therapeutic intervention in a disease associated with altered mitochondrial function. Moreover, functional classifications of these proteins as recited in Tables 1 and 2 and in the GenBank annotations cited therein (which are incorporated by reference) provides further guidance to those familiar with the art regarding how readily and without undue experimentation to select a biological activity for interrogation, to determine whether such activity is altered in a sample according to art accepted methodologies.

According to certain embodiments of the invention, a mitochondrial polypeptide is isolated from a biological sample following exposure of the sample to a "biological stimulus", which may include any naturally occurring or artificial (including recombinant) compound that is capable of inducing altered biological activity of a mitochondrial molecular component which is, in preferred embodiments, a mitochondrial polypeptide. Thus, a biological stimulus may be employed, according to certain of the subject invention methods, to effect a perturbation of the biological status of a cell in a manner that alters biological activity of a mitochondrial polypeptide, such that the altered activity can be detected using any methodology described or referred to herein or known to the art, for example, according to the mass spectrometric fingerprinting methods described herein and in the cited references. Non-limiting examples of biological stimuli include antibodies, hormones, cytokines, chemokines, biologically active polypeptides and peptides and other soluble mediators, apoptogens, signal transduction agents, small molecules, cations and ionophores, physical and chemical stressors, and the like.

The polypeptides of the present invention are preferably provided in an isolated form, and in certain preferred embodiments are purified to homogeneity. The terms "fragment," "derivative" and "analog" when referring to mitochondrial proteins such as polypeptides identified herein as mitochondrial components and having amino acid sequences as set forth in at least one of SEQ ID NOS:1-3025, or when referring to modified polypeptides that comprise at least one modification to a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS:1-3025 as provided herein, refers to any polypeptide or protein that retains essentially the same biological function or activity as such polypeptide. Thus, an analog includes a proprotein which can be activated by cleavage of the proprotein portion to produce an active polypeptide.

The polypeptide (*e.g.*, a human mitochondrial protein or polypeptide having an amino acid sequence set forth in SEQ ID NOS:1-3025) of the present invention may be a naturally occurring, a recombinant polypeptide or a synthetic polypeptide, and is preferably an isolated, naturally occurring polypeptide. Modified polypeptides according to the present invention comprise at least one modification (*e.g.*, a structural change that occurs with statistical significance in a disease associated with altered mitochondrial function) to a protein or polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS:1-3025. The protein or polypeptide may therefore be an unmodified polypeptide or may be a polypeptide that has been posttranslationally modified, for example by glycosylation (*e.g.,* N-linked glycosylation via asparagines residues, or O-linked glycoslyation via serine or threonine residues or post-biosynthetic glycation, etc.), phosphorylation, oxidation or oxidative modification, nitration, nitrosylation, amidation, fatty acylation including glycosylphosphatidylinositol anchor modification or the like, phospholipase cleavage such as phosphatidylinositol-specific phospholipase c mediated hydrolysis or the like, protease cleavage, dephosphorylation or any other type of protein posttranslational modification such as a modification involving formation or cleavage of a covalent chemical bond, although the invention need not be so limited and also contemplates non-covalent associations of proteins with other biomolecules (*e.g.*, lipoproteins,

metalloproteins, etc.). Methods for determining the presence of such modifications are well known in the art (*e.g.,* Scopes, R.K., *Protein Purification: Principles and Practice*, 1987, Springer-Verlag, NY; Angeletti, Ed., *Techniques in Protein Chemistry III*, Academic Press, Inc., New York, 1993; Baynes et al., 1991 *Diabetes* 40:405; Baynes et al., 1999 *Diabetes* 48:1; Yamakura et al., 1998 *J. Biol. Chem.* 273:14085; MacMillan et al., 1998 *Biochem.* 37:1613; see also PCT/US01/14066).

A fragment, derivative or analog of a mitochondrial molecular component polypeptide or protein may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, which may include a posttranslational modification or an adduct (*e.g.*, an oxidative adduct), or (iii) one in which one or more of the amino acid residues are deleted, or (iv) one in which additional amino acids are fused to the polypeptide, including a signal sequence, a leader sequence or a proprotein sequence or the like, and also including additional peptide or non-peptide moieties that may be added to proteins such as ubiquitin, glutathione, thioredoxin and the like. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

The polypeptides of the present invention include mitochondrial polypeptides and proteins having amino acid sequences that are identical or similar to sequences known in the art. As known in the art "similarity" between two polypeptides is determined by comparing the amino acid sequence and conserved amino acid substitutes thereto of the polypeptide to the sequence of a second polypeptide. Fragments or portions of the polypeptides of the present invention may be employed for producing the corresponding full-length polypeptide by peptide synthesis; therefore, the fragments may be employed as intermediates for producing the full-length polypeptides.

As described herein, isolation of a mitochondrial polypeptide component such as a mitochondrial molecular component with which an agent

identified according to the methods of the invention interacts refers to physical separation of such a complex from its biological source, and may be accomplished by any of a number of well known techniques including but not limited to those described herein, and in the cited references. Without wishing to be bound by theory, a compound that "binds a mitochondrial component" can be any discrete molecule, agent compound, composition of matter or the like that may, but need not, directly bind to a mitochondrial molecular component, and may in the alternative bind indirectly to a mitochondrial molecular component by interacting with one or more additional components that bind to a mitochondrial molecular component. These or other mechanisms by which a compound may bind to and/or associate with a mitochondrial molecular component are within the scope of the claimed methods. Binding to a mitochondrial component may under certain conditions result in altered biological activity of the mitochondrial component.

According to certain preferred embodiments of the present invention, proteins and polypeptides comprising one or more of the amino acid sequences set forth in SEQ ID NOS:1-3025, which include polypeptides not previously known to be mitochondrial components, may be targets for drug screening and/or for therapeutic intervention. A "target" refers to a biochemical entity involved in a biological process, typically a protein that plays a useful role in the physiology or biology of a subject or biological source. A therapeutic composition or compound may bind to, alter the conformation of, impair or enhance the activity of or otherwise influence a target to alter (*e.g.,* increase or decrease in a statistically significant manner relative to an appropriate untreated control) its function. As used herein, targets can include, but need not be limited to, proteins having a mitochondrial function classification as summarized in Table 2 and as described in greater detail below.

For example, targets may include proteins that are components of, or that associate with, mitochondrial ETC complexes, Krebs cycle or TCA cycle components including any molecules functionally linked (*e.g.*, as substrates, cofactors, intermediates, biochemical donor or acceptor species, or the like) to such components, transport protein or carrier protein assemblies, factors or

complexes involved in DNA (including mtDNA) replication or transcription or in translation of mRNA, cellular receptors, G-proteins or G-protein coupled receptors, kinases, phosphatases, ion channels, lipases, phosholipases, nuclear receptors and factors, intracellular structures, components of signal transduction and apoptotic pathways, and the like.

Methods for identifying a mitochondrial target (*e.g.*, a pharmaceutical target such as a target for therapeutic intervention in a disease associated with altered mitochondrial function as provided herein, for instance, diabetes mellitus, a neurodegenerative disease, a disease associated with inappropriate cell proliferation or cell survival, or a cardiovascular condition) include providing a compound that modulates expression level, structure and/or activity of a particular mitochondrial protein (*e.g.*, a component of the human mitochondrial proteome such as any one or more of the proteins having amino acid sequences set forth in SEQ ID NOS:1-3025) and identifying the cellular component(s) that binds to the compound to form a molecular complex, preferably through a specific interaction.

"Altered mitochondrial function" may refer to any condition or state, including those that accompany a disease associated with altered mitochondrial function, where any structure or activity that is directly or indirectly related to a mitochondrial function has been changed in a statistically significant manner relative to a control or standard. Altered mitochondrial function may have its origin in extramitochondrial structures or events as well as in mitochondrial structures or events, in direct interactions between mitochondrial and extramitochondrial genes and/or their gene products, or in structural or functional changes that occur as the result of interactions between intermediates that may be formed as the result of such interactions, including metabolites, catabolites, substrates, precursors, cofactors and the like.

Additionally, altered mitochondrial function may include altered respiratory, metabolic or other biochemical or biophysical activity in one or more cells of a biological sample or a biological source. As non-limiting examples, markedly impaired ETC activity may be related to altered mitochondrial function, as may be generation of increased reactive oxygen species (ROS) or defective

oxidative phosphorylation. As further examples, altered mitochondrial membrane potential, induction of apoptotic pathways and formation of atypical chemical and biochemical crosslinked species within a cell, whether by enzymatic or non-enzymatic mechanisms, may all be regarded as indicative of altered mitochondrial function. These and other non-limiting examples of altered mitochondrial function are contemplated by the present invention.

For instance, altered mitochondrial function may be related, *inter alia*, to altered intracellular calcium regulation that may accompany loss of mitochondrial membrane electrochemical potential by intracellular calcium flux, by mechanisms that include free radical oxidation, defects in transmitochondrial membrane shuttles and transporters such as the adenine nucleotide transporter or the malate-aspartate shuttle, by defects in ATP biosynthesis, by impaired association of hexokinases and/or other enzymes with porin at the inner mitochondrial membrane, or by other events. Altered intracellular calcium regulation and/or collapse of mitochondrial inner membrane potential may result from direct or indirect effects of mitochondrial genes, gene products or related downstream mediator molecules and/or extramitochondrial genes, gene products or related downstream mediators, or from other known or unknown causes.

Thus, an "indicator of altered mitochondrial function" may be any detectable parameter that directly relates to a condition, process, pathway, dynamic structure, state or other activity involving mitochondria and that permits detection of altered mitochondrial function in a biological sample from a subject or biological source. According to non-limiting theory, altered mitochondrial function therefore may also include altered mitochondrial permeability to calcium or to mitochondrial molecular components involved in apoptosis (*e.g.*, cytochrome c), or other alterations in mitochondrial respiration, or any other altered biological activity as provided herein that is a mitochondrially associated activity.

In certain preferred embodiments of the invention, an enzyme is the indicator of altered mitochondrial function as provided herein. The enzyme may be a mitochondrial enzyme, which may further be an ETC enzyme or a Krebs cycle enzyme. The enzyme may also be an ATP biosynthesis factor, which may include

an ETC enzyme and/or a Krebs cycle enzyme, or other enzymes or cellular components related to ATP production as provided herein. A "non-enzyme" refers to an indicator of altered mitochondrial function that is not an enzyme (*i.e.,* that is not a mitochondrial enzyme or an ATP biosynthesis factor as provided herein). In certain other preferred embodiments, an enzyme is a co-indicator of altered mitochondrial function. The following enzymes may not be indicators of altered mitochondrial function according to the present invention, but may be co-indicators of altered mitochondrial function as provided herein: citrate synthase (EC 4.1.3.7), hexokinase II (EC 2.7.1.1; see, *e.g.,* Kruszynska et al. 1998), cytochrome c oxidase (EC 1.9.3.1), phosphofructokinase (EC 2.7.1.11), glyceraldehyde phosphate dehydrogenase (EC 1.2.1.12), glycogen phosphorylase (EC 2.4.1.1) creatine kinase (EC 2.7.3.2), NADH dehydrogenase (EC 1.6.5.3), glycerol 3-phosphate dehydrogenase (EC 1.1.1.8), triose phosphate dehydrogenase (EC 1.2.1.12) and malate dehydrogenase (EC 1.1.1.37).

In other highly preferred embodiments, the indicator of altered mitochondrial function is any ATP biosynthesis factor as described below. In other preferred embodiments, the indicator is ATP production. In other preferred embodiments, the indicator of altered mitochondrial function may be mitochondrial mass or mitochondrial number. According to the present invention, mitochondrial DNA content may not be an indicator of altered mitochondrial function but may be a co-predictor of altered mitochondrial function or a co-indicator of altered mitochondrial function, as provided herein. In other preferred embodiments the indicator of altered mitochondrial function may be free radical production, a cellular response to elevated intracellular calcium or a cellular response to an apoptogen.

INDICATORS OF ALTERED MITOCHONDRIAL FUNCTION THAT ARE ENZYMES

As provided herein, in certain preferred embodiments, an altered biological activity comprises an indicator of altered mitochondrial function that may be an enzyme; such an enzyme may be a mitochondrial enzyme or an ATP biosynthesis factor that is an enzyme, for example an ETC enzyme or a Krebs cycle enzyme.

Reference herein to "enzyme quantity", "enzyme catalytic activity" or "enzyme expression level" is meant to include a reference to any of a mitochondrial enzyme quantity, activity or expression level or an ATP biosynthesis factor quantity, activity or expression level; either of which may further include, for example, an ETC enzyme quantity, activity or expression level or a Krebs cycle enzyme quantity, activity or expression level. In the most preferred embodiments of the invention, an enzyme is a natural or recombinant protein or polypeptide that has enzyme catalytic activity as provided herein. Such an enzyme may be, by way of non-limiting examples, an enzyme, a holoenzyme, an enzyme complex, an enzyme subunit, an enzyme fragment, derivative or analog or the like, including a truncated, processed or cleaved enzyme.

A "mitochondrial enzyme" that may be an indicator of altered mitochondrial function as provided herein refers to a mitochondrial molecular component that has enzyme catalytic activity and/or functions as an enzyme cofactor capable of influencing enzyme catalytic activity. As used herein, mitochondria are comprised of "mitochondrial molecular components", which may be a protein, polypeptide, peptide, amino acid, or derivative thereof; a lipid, fatty acid or the like, or derivative thereof; a carbohydrate, saccharide or the like or derivative thereof, a nucleic acid, nucleotide, nucleoside, purine, pyrimidine or related molecule, or derivative thereof, or the like; or any covalently or non-covalently complexed combination of these components, or any other biological molecule that is a stable or transient constituent of a mitochondrion.

A mitochondrial enzyme that may be an indicator of altered mitochondrial function or a co-indicator of altered mitochondrial function as provided herein, or an ATP biosynthesis factor that may be an indicator of altered mitochondrial function as provided herein, may comprise an ETC enzyme, which refers to any mitochondrial molecular component that is a mitochondrial enzyme component of the mitochondrial electron transport chain (ETC) complex associated with the inner mitochondrial membrane and mitochondrial matrix. An ETC enzyme may include any of the multiple ETC subunit polypeptides encoded by mitochondrial and nuclear genes. The ETC is typically described as comprising

complex I (NADH:ubiquinone reductase), complex II (succinate dehydrogenase), complex III (ubiquinone: cytochrome c oxidoreductase), complex IV (cytochrome c oxidase) and complex V (mitochondrial ATP synthetase), where each complex includes multiple polypeptides and cofactors (for review see, *e.g.,* Walker et al., 1995 *Meths. Enzymol.* 260:14; Ernster et al., 1981 *J. Cell Biol.* 91:227s-255s, and references cited therein).

A mitochondrial enzyme that may be an indicator of altered mitochondrial function as provided herein, or an ATP biosynthesis factor that may be an indicator of altered mitochondrial function as provided herein, may also comprise a Krebs cycle enzyme, which includes mitochondrial molecular components that mediate the series of biochemical/ bioenergetic reactions also known as the citric acid cycle or the tricarboxylic acid cycle (see, *e.g.,* Lehninger, Biochemistry, 1975 Worth Publishers, NY; Voet and Voet, Biochemistry, 1990 John Wiley & Sons, NY; Mathews and van Holde, Biochemistry, 1990 Benjamin Cummings, Menlo Park, CA). Krebs cycle enzymes include subunits and cofactors of citrate synthase, aconitase, isocitrate dehydrogenase, the α-ketoglutarate dehydrogenase complex, succinyl CoA synthetase, succinate dehydrogenase, fumarase and malate dehydrogenase. Krebs cycle enzymes further include enzymes and cofactors that are functionally linked to the reactions of the Krebs cycle, such as, for example, nicotinamide adenine dinucleotide, coenzyme A, thiamine pyrophosphate, lipoamide, guanosine diphosphate, flavin adenine dinucloetide, acetyl-coA carboxylase (ACC) and nucleoside diphosphokinase.

The methods of the present invention also pertain in part to the correlation of mitochondrial associated disease with an indicator of altered mitochondrial function that may be an ATP biosynthesis factor, an altered amount of ATP or an altered amount of ATP production.

An "ATP biosynthesis factor " refers to any naturally occurring cellular component that contributes to the efficiency of ATP production in mitochondria. Such a cellular component may be a protein, polypeptide, peptide, amino acid, or derivative thereof; a lipid, fatty acid or the like, or derivative thereof; a carbohydrate, saccharide or the like or derivative thereof, a nucleic acid,

nucleotide, nucleoside, purine, pyrimidine or related molecule, or derivative thereof, or the like. An ATP biosynthesis factor includes at least the components of the ETC and of the Krebs cycle (see, *e.g.,* Lehninger, Biochemistry, 1975 Worth Publishers, NY; Voet and Voet, Biochemistry, 1990 John Wiley & Sons, NY; Mathews and van Holde, Biochemistry, 1990 Benjamin Cummings, Menlo Park, CA) and any protein, enzyme or other cellular component that participates in ATP synthesis, regardless of whether such ATP biosynthesis factor is the product of a nuclear gene or of an extranuclear gene (*e.g.,* a mitochondrial gene). Participation in ATP synthesis may include, but need not be limited to, catalysis of any reaction related to ATP synthesis, transmembrane import and/or export of ATP or of an enzyme cofactor, transcription of a gene encoding a mitochondrial enzyme and/or translation of such a gene transcript.

Compositions and methods for determining whether a cellular component is an ATP biosynthesis factor are well known in the art, and include methods for determining ATP production (including determination of the rate of ATP production in a sample) and methods for quantifying ATP itself. The contribution of an ATP biosynthesis factor to ATP production can be determined, for example, using an isolated ATP biosynthesis factor that is added to cells or to a cell-free system. The ATP biosynthesis factor may directly or indirectly mediate a step or steps in a biosynthetic pathway that influences ATP production. For example, an ATP biosynthesis factor may be an enzyme that catalyzes a particular chemical reaction leading to ATP production. As another example, an ATP biosynthesis factor may be a cofactor that enhances the efficiency of such an enzyme. As another example, an ATP biosynthesis factor may be an exogenous genetic element introduced into a cell or a cell-free system that directly or indirectly affects an ATP biosynthetic pathway. Those having ordinary skill in the art are readily able to compare ATP production by an ATP biosynthetic pathway in the presence and absence of a candidate ATP biosynthesis factor. Routine determination of ATP production may be accomplished using any known method for quantitative ATP detection, for example by way of illustration and not limitation, by differential extraction from a sample optionally including chromatographic

isolation; by spectrophotometry; by quantification of labeled ATP recovered from a sample contacted with a suitable form of a detectably labeled ATP precursor molecule such as, for example, ^{32}P; by quantification of an enzyme activity associated with ATP synthesis or degradation; or by other techniques that are known in the art. Accordingly, in certain embodiments of the present invention, the amount of ATP in a biological sample or the production of ATP (including the rate of ATP production) in a biological sample may be an indicator of altered mitochondrial function. In one embodiment, for instance, ATP may be quantified by measuring luminescence of luciferase catalyzed oxidation of D-luciferin, an ATP dependent process.

"Enzyme catalytic activity" refers to any function performed by a particular enzyme or category of enzymes that is directed to one or more particular cellular function(s). For example, "ATP biosynthesis factor catalytic activity" refers to any function performed by an ATP biosynthesis factor as provided herein that contributes to the production of ATP. Typically, enzyme catalytic activity is manifested as facilitation of a chemical reaction by a particular enzyme, for instance an enzyme that is an ATP biosynthesis factor, wherein at least one enzyme substrate or reactant is covalently modified to form a product. For example, enzyme catalytic activity may result in a substrate or reactant being modified by formation or cleavage of a covalent chemical bond, but the invention need not be so limited. Various methods of measuring enzyme catalytic activity are known to those having ordinary skill in the art and depend on the particular activity to be determined.

For many enzymes, including mitochondrial enzymes or enzymes that are ATP biosynthesis factors as provided herein, quantitative criteria for enzyme catalytic activity are well established. These criteria include, for example, activity that may be defined by international units (IU), by enzyme turnover number, by catalytic rate constant (K_{cat}), by Michaelis-Menten constant (K_m), by specific activity or by any other enzymological method known in the art for measuring a level of at least one enzyme catalytic activity. Specific activity of a mitochondrial enzyme, such as an ATP biosynthesis factor, may be expressed as

units of substrate detectably converted to product per unit time and, optionally, further per unit sample mass (*e.g.*, per unit protein or per unit mitochondrial mass).

In certain preferred embodiments of the invention, enzyme catalytic activity may be expressed as units of substrate detectably converted by an enzyme to a product per unit time per unit total protein in a sample. In certain particularly preferred embodiments, enzyme catalytic activity may be expressed as units of substrate detectably converted by an enzyme to product per unit time per unit mitochondrial mass in a sample. In certain highly preferred embodiments, enzyme catalytic activity may be expressed as units of substrate detectably converted by an enzyme to product per unit time per unit mitochondrial protein mass in a sample. Products of enzyme catalytic activity may be detected by suitable methods that will depend on the quantity and physicochemical properties of the particular product. Thus, detection may be, for example by way of illustration and not limitation, by radiometric, colorimetric, spectrophotometric, fluorimetric, immunometric or mass spectrometric procedures, or by other suitable means that will be readily apparent to a person having ordinary skill in the art.

In certain embodiments of the invention, detection of a product of enzyme catalytic activity may be accomplished directly, and in certain other embodiments detection of a product may be accomplished by introduction of a detectable reporter moiety or label into a substrate or reactant such as a marker enzyme, dye, radionuclide, luminescent group, fluorescent group or biotin, or the like. The amount of such a label that is present as unreacted substrate and/or as reaction product, following a reaction to assay enzyme catalytic activity, is then determined using a method appropriate for the specific detectable reporter moiety or label. For radioactive groups, radionuclide decay monitoring, scintillation counting, scintillation proximity assays (SPA) or autoradiographic methods are generally appropriate. For immunometric measurements, suitably labeled antibodies may be prepared including, for example, those labeled with radionuclides, with fluorophores, with affinity tags, with biotin or biotin mimetic sequences or those prepared as antibody-enzyme conjugates (see, *e.g.*, Weir, D.M., *Handbook of Experimental Immunology*, 1986, Blackwell Scientific, Boston;

Scouten, W.H., *Methods in Enzymology 135*:30-65, 1987; Harlow and Lane, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory, 1988; Haugland, 1996 *Handbook of Fluorescent Probes and Research Chemicals- Sixth Ed.*, Molecular Probes, Eugene, OR; Scopes, R.K., *Protein Purification: Principles and Practice*, 1987, Springer-Verlag, NY; Hermanson, G.T. et al., *Immobilized Affinity Ligand Techniques*, 1992, Academic Press, Inc., NY; Luo et al., 1998 *J. Biotechnol.* 65:225 and references cited therein). Spectroscopic methods may be used to detect dyes (including, for example, colorimetric products of enzyme reactions), luminescent groups and fluorescent groups. Biotin may be detected using avidin or streptavidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic, spectrophotometric or other analysis of the reaction products. Standards and standard additions may be used to determine the level of enzyme catalytic activity in a sample, using well known techniques.

As noted above, enzyme catalytic activity of an ATP biosynthesis factor may further include other functional activities that lead to ATP production, beyond those involving covalent alteration of a substrate or reactant. For example by way of illustration and not limitation, an ATP biosynthesis factor that is an enzyme may refer to a transmembrane transporter molecule that, through its enzyme catalytic activity, facilitates the movement of metabolites between cellular compartments. Such metabolites may be ATP or other cellular components involved in ATP synthesis, such as gene products and their downstream intermediates, including metabolites, catabolites, substrates, precursors, cofactors and the like. As another non-limiting example, an ATP biosynthesis factor that is an enzyme may, through its enzyme catalytic activity, transiently bind to a cellular component involved in ATP synthesis in a manner that promotes ATP synthesis. Such a binding event may, for instance, deliver the cellular component to another enzyme involved in ATP synthesis and/or may alter the conformation of the cellular component in a manner that promotes ATP synthesis. Further to this example, such conformational alteration may be part of a signal transduction pathway, an

allosteric activation pathway, a transcriptional activation pathway or the like, where an interaction between cellular components leads to ATP production.

Thus, according to the present invention, an ATP biosynthesis factor may include, as non-limiting examples, an ATP synthase, acetyl-coA carboxylase (ACC) a mitochondrial matrix protein and a mitochondrial membrane protein. Suitable mitochondrial membrane proteins include such mitochondrial components as the adenine nucleotide transporter (ANT; *e.g.,* Fiore et al., 1998 *Biochimie* 80:137; Klingenberg 1985 *Ann. N.Y.Acad. Sci.* 456:279), the voltage dependent anion channel (VDAC, also referred to as porin; *e.g.,* Manella, 1997 *J. Bioenergetics Biomembr.* 29:525), the malate-aspartate shuttle, the mitochondrial calcium uniporter (*e.g.,* Litsky et al., 1997 *Biochem.* 36:7071), uncoupling proteins (UCP-1, -2, -3; see *e.g.,* Jezek et al., 1998 *Int. J. Biochem. Cell Biol.* 30:1163), a hexokinase, a peripheral benzodiazepine receptor, a mitochondrial intermembrane creatine kinase, cyclophilin D, a Bcl-2 gene family encoded polypeptide, the tricarboxylate carrier (*e.g.,* Iacobazzi et al., 1996 Biochim. Biophys. Acta 1284:9; Bisaccia et al., 1990 Biochim. Biophys. Acta 1019:250) and the dicarboxylate carrier (*e.g.,* Fiermonte et al., 1998 *J. Biol. Chem.* 273:24754; Indiveri et al., 1993 *Biochim. Biophys. Acta* 1143:310; for a general review of mitochondrial membrane transporters, see, *e.g.,* Zoratti et al., 1994 *J. Bioenergetics Biomembr.* 26:543 and references cited therein).

"Enzyme quantity" as used herein refers to an amount of an enzyme including mitochondrial enzymes or enzymes that are ATP biosynthesis factors as provided herein, or of another ATP biosynthesis factor, that is present, *i.e.,* the physical presence of an enzyme or ATP biosynthesis factor selected as an indicator of altered mitochondrial function, irrespective of enzyme catalytic activity. Depending on the physicochemical properties of a particular enzyme or ATP biosynthesis factor, the preferred method for determining the enzyme quantity will vary. In the most highly preferred embodiments of the invention, determination of enzyme quantity will involve quantitative determination of the level of a protein or polypeptide using routine methods in protein chemistry with which those having

skill in the art will be readily familiar, for example by way of illustration and not limitation, those described in greater detail below.

Accordingly, determination of enzyme quantity may be by any suitable method known in the art for quantifying a particular cellular component that is an enzyme or an ATP biosynthesis factor as provided herein, and that in preferred embodiments is a protein or polypeptide. Depending on the nature and physicochemical properties of the enzyme or ATP biosynthesis factor, determination of enzyme quantity may be by densitometric, mass spectrometric, spectrophotometric, fluorimetric, immunometric, chromatographic, electrochemical or any other means of quantitatively detecting a particular cellular component. Methods for determining enzyme quantity also include methods described above that are useful for detecting products of enzyme catalytic activity, including those measuring enzyme quantity directly and those measuring a detectable label or reporter moiety. In certain preferred embodiments of the invention, enzyme quantity is determined by immunometric measurement of an isolated enzyme or ATP biosynthesis factor . In certain preferred embodiments of the invention, these and other immunological and immunochemical techniques for quantitative determination of biomolecules such as an enzyme or ATP biosynthesis factor may be employed using a variety of assay formats known to those of ordinary skill in the art, including but not limited to enzyme linked immunosorbent assay (ELISA), radioimmunoassay (RIA), immunofluorimetry, immunoprecipitation, equilibrium dialysis, immunodiffusion and other techniques. (*See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory, 1988; Weir, D.M., *Handbook of Experimental Immunology*, 1986, Blackwell Scientific, Boston.) For example, the assay may be performed in a Western blot format, wherein a preparation comprising proteins from a biological sample is submitted to gel electrophoresis, transferred to a suitable membrane and allowed to react with an antibody specific for an enzyme or an ATP biosynthesis factor that is a protein or polypeptide. The presence of the antibody on the membrane may then be detected using a suitable detection reagent, as is well known in the art and described above.

INDICATORS OF ALTERED MITOCHONDRIAL FUNCTION THAT ARE CELLULAR RESPONSES TO ELEVATED INTRACELLULAR CALCIUM

According to certain embodiments of the present invention, a method is provided that comprises in pertinent part determining a biological activity of a mitochondrial polypeptide by monitoring intracellular calcium homeostasis and/or cellular responses to perturbations of this homeostasis, including physiological and pathophysiological calcium regulation. In particular, according to these embodiments, the method of the present invention is directed to comparing a cellular response to elevated intracellular calcium in a biological sample in the presence and absence of a candidate agent, or to comparing such a response in a sample from a subject known or suspected of having a disease associated with altered mitochondrial function with that of a control subject. The range of cellular responses to elevated intracellular calcium is broad, as is the range of methods and reagents for the detection of such responses. Many specific cellular responses are known to those having ordinary skill in the art; these responses will depend on the particular cell types present in a selected biological sample. It is within the contemplation of the present invention to provide a method comprising comparing a cellular response to elevated intracellular calcium, where such response is an indicator of altered mitochondrial function as provided herein. As non-limiting examples, cellular responses to elevated intracellular calcium include secretion of specific secretory products, exocytosis of particular pre-formed components, increased glycogen metabolism and cell proliferation (see, *e.g.*, Clapham, 1995 *Cell* 80:259; Cooper, *The Cell - A Molecular Approach*, 1997 ASM Press, Washington, D.C.; Alberts, B., Bray, D., et al., *Molecular Biology of the Cell*, 1995 Garland Publishing, NY).

As a brief background, normal alterations of intramitochondrial Ca^{2+} are associated with normal metabolic regulation (Dykens, 1998 in *Mitochondria & Free Radicals in Neurodegenerative Diseases*, Beal, Howell and Bodis-Wollner, Eds., Wiley-Liss, New York, pp. 29-55; Radi et al., 1998 in *Mitochondria & Free Radicals in Neurodegenerative Diseases*, Beal, Howell and Bodis-Wollner, Eds.,

Wiley-Liss, New York, pp. 57-89; Gunter and Pfeiffer, 1991, *Am. J. Physiol. 27*: C755; Gunter et al., 1994, Am. J. Physiol. 267: 313). For example, fluctuating levels of mitochondrial free Ca^{2+} may be responsible for regulating oxidative metabolism in response to increased ATP utilization, via allosteric regulation of enzymes (reviewed by Crompton et al., 1993 *Basic Res. Cardiol. 88*: 513-523;) and the glycerophosphate shuttle (Gunter et al., 1994 *J. Bioenerg. Biomembr. 26*: 471).

Normal mitochondrial function includes regulation of cytosolic free calcium levels by sequestration of excess Ca^{2+} within the mitochondrial matrix. Depending on cell type, cytosolic Ca^{2+} concentration is typically 50-100 nM. In normally functioning cells, when Ca^{2+} levels reach 200-300 nM, mitochondria begin to accumulate Ca^{2+} as a function of the equilibrium between influx via a Ca^{2+} uniporter in the inner mitochondrial membrane and Ca^{2+} efflux via both Na^+ dependent and Na^+independent calcium carriers. In certain instances, such perturbation of intracellular calcium homeostasis is a feature of diseases associated with altered mitochondrial function, regardless of whether the calcium regulatory dysfunction is causative of, or a consequence of, altered mitochondrial function.

Elevated mitochondrial calcium levels thus may accumulate in response to an initial elevation in cytosolic free calcium, as described above. Such elevated mitochondrial calcium concentrations in combination with reduced ATP or other conditions associated with mitochondrial pathology, can lead to collapse of mitochondrial inner membrane potential (see Gunter et al., 1998 *Biochim. Biophys. Acta 1366*:5; Rottenberg and Marbach, 1990, *Biochim. Biophys. Acta 1016*:87). Generally, in order to practice the subject invention methods, the extramitochondrial (cytosolic) level of Ca^{2+} in a biological sample is greater than that present within mitochondria. For example, in the case of type 2 diabetes mellitus (type 2 DM), mitochondrial or cytosolic calcium levels may vary from the above ranges and may range from, *e.g.,* about 1 nM to about 500 mM, more typically from about 10 nM to about 100 μM and usually from about 20 nM to about 1 μM, where "about" indicates ± 10%. A variety of calcium indicators are known in

the art, including but not limited to, for example, fura-2 (McCormack et al., 1989 *Biochim. Biophys. Acta 973*:420); mag-fura-2; BTC (U.S. Patent No. 5,501,980); fluo-3, fluo-4 and fluo-5N (U.S. Patent No. 5,049,673); rhod-2; benzothiaza-1; and benzothiaza-2 (all of which are available from Molecular Probes, Eugene, OR). These or any other means for monitoring intracellular calcium are contemplated according to the subject invention method for identifying a risk for type 2 DM.

For monitoring an indicator of altered mitochondrial function that is a cellular response to elevated intracellular calcium, compounds that induce increased cytoplasmic and mitochondrial concentrations of Ca^{2+}, including calcium ionophores, are well known to those of ordinary skill in the art, as are methods for measuring intracellular calcium and intramitochondrial calcium (*see, e.g.*, Gunter and Gunter, 1994 *J. Bioenerg. Biomembr. 26*: 471; Gunter et al., 1998 *Biochim. Biophys. Acta 1366*:5; McCormack et al., 1989 *Biochim. Biophys. Acta 973*:420; Orrenius and Nicotera, 1994 *J. Neural. Transm. Suppl. 43*:1; Leist and Nicotera, 1998 *Rev. Physiol. Biochem. Pharmacol. 132*:79; and Haugland, 1996 *Handbook of Fluorescent Probes and Research Chemicals- Sixth Ed.*, Molecular Probes, Eugene, OR) . Accordingly, a person skilled in the art may readily select a suitable ionophore (or another compound that results in increased cytoplasmic and/or mitochondrial concentrations of Ca^{2+}) and an appropriate means for detecting intracellular and/or intramitochondrial calcium for use in the present invention, according to the instant disclosure and to well known methods.

Ca^{2+} influx into mitochondria appears to be largely dependent, and may be completely dependent, upon the negative transmembrane electrochemical potential ($\Delta\Psi$) established at the inner mitochondrial membrane by electron transfer, and such influx fails to occur in the absence of $\Delta\Psi$ even when an eight-fold Ca^{2+} concentration gradient is imposed (Kapus et al., 1991 *FEBS Lett.* 282:61). Accordingly, mitochondria may release Ca^{2+} when the membrane potential is dissipated, as occurs with uncouplers like 2,4-dinitrophenol and carbonyl cyanide p-trifluoro-methoxyphenylhydrazone (FCCP). Thus, according to certain embodiments of the present invention, collapse of $\Delta\Psi$ may be potentiated by influxes of cytosolic free calcium into the mitochondria, as may occur under

certain physiological conditions including those encountered by cells of a subject having type 2 DM. Detection of such collapse may be accomplished by a variety of means as provided herein.

Typically, mitochondrial membrane potential may be determined according to methods with which those skilled in the art will be readily familiar, including but not limited to detection and/or measurement of detectable compounds such as fluorescent indicators, optical probes and/or sensitive pH and ion-selective electrodes (*See, e.g.,* Ernster et al., 1981 *J. Cell Biol. 91*:227s and references cited; *see also* Haugland, 1996 *Handbook of Fluorescent Probes and Research Chemicals- Sixth Ed.*, Molecular Probes, Eugene, OR, pp. 266-274 and 589-594.). For example, by way of illustration and not limitation, the fluorescent probes 2-,4-dimethylaminostyryl-N-methyl pyridinium (DASPMI) and tetramethylrhodamine esters (such as, *e.g.*, tetramethylrhodamine methyl ester, TMRM; tetramethylrhodamine ethyl ester, TMRE) or related compounds (*see, e.g.,* Haugland, 1996, *supra*) may be quantified following accumulation in mitochondria, a process that is dependent on, and proportional to, mitochondrial membrane potential (*see, e.g.,* Murphy et al., 1998 in *Mitochondria & Free Radicals in Neurodegenerative Diseases*, Beal, Howell and Bodis-Wollner, Eds., Wiley-Liss, New York, pp. 159-186 and references cited therein; and *Molecular Probes On-line Handbook of Fluorescent Probes and Research Chemicals,* at http://www.probes.com/handbook/toc.html). Other fluorescent detectable compounds that may be used in the invention include but are not limited to rhodamine 123, rhodamine B hexyl ester, $DiOC_6(3)$, JC-1 [5,5',6,6'-Tetrachloro-1,1',3,3'-Tetraethylbezimidazolcarbocyanine Iodide] (*see* Cossarizza, et al., 1993 *Biochem. Biophys. Res. Comm. 197*:40; Reers et al., 1995 *Meth. Enzymol. 260*:406), rhod-2 (*see* U.S. Patent No. 5,049,673; all of the preceding compounds are available from Molecular Probes, Eugene, Oregon) and rhodamine 800 (Lambda Physik, GmbH, Göttingen, Germany; *see* Sakanoue et al., 1997 *J. Biochem. 121*:29). Methods for monitoring mitochondrial membrane potential are also disclosed in U.S. Application No. 09/161,172.

Mitochondrial membrane potential can also be measured by non-fluorescent means, for example by using TTP (tetraphenylphosphonium ion) and a TTP-sensitive electrode (Kamo et al., 1979 *J. Membrane Biol. 49*:105; Porter and Brand, 1995 *Am. J. Physiol. 269*:R1213). Those skilled in the art will be able to select appropriate detectable compounds or other appropriate means for measuring $\Delta\Psi m$. By way of example and not limitation, TMRM is somewhat preferable to TMRE because, following efflux from mitochondria, TMRE yields slightly more residual signal in the endoplasmic reticulicum and cytoplasm than TMRM.

As another non-limiting example, membrane potential may be additionally or alternatively calculated from indirect measurements of mitochondrial permeability to detectable charged solutes, using matrix volume and/or pyridine nucleotide redox determination combined with spectrophotometric or fluorimetric quantification. Measurement of membrane potential dependent substrate exchange-diffusion across the inner mitochondrial membrane may also provide an indirect measurement of membrane potential. (*See, e.g.,* Quinn, 1976, *The Molecular Biology of Cell Membranes*, University Park Press, Baltimore, Maryland, pp. 200-217 and references cited therein.)

Exquisite sensitivity to extraordinary mitochondrial accumulations of Ca^{2+} that result from elevation of intracellular calcium, as described above, may also characterize type 2 DM. Such mitochondrial sensitivity may provide an indicator of altered mitochondrial function according to the present invention. Additionally, a variety of physiologically pertinent agents, including hydroperoxide and free radicals, may synergize with Ca^{2+} to induce collapse of $\Delta\Psi$ (Novgorodov et al., 1991 *Biochem. Biophys. Acta 1058*: 242; Takeyama et al., 1993 *Biochem. J. 294:* 719; Guidox et al., 1993 *Arch. Biochem. Biophys. 306*:139).

INDICATORS OF ALTERED MITOCHONDRIAL FUNCTION THAT ARE CELLULAR RESPONSES TO APOPTOGENIC STIMULI

Turning to another aspect, the present invention relates to the correlation of diseases associated with altered mitochondrial function with an

indicator of altered mitochondrial function, involving programmed cell death or apoptosis. In particular, according to this aspect, the present invention is directed to a method comprising comparing a cellular response to an apoptosis-inducing ("apoptogenic") stimulus in a biological sample from (i) a subject believed to be at risk for disease, and (ii) a control subject. The range of cellular responses to various known apoptogenic stimuli is broad, as is the range of methods and reagents for the detection of such responses. It is within the contemplation of the present invention to provide a method for identifying a risk for disease by comparing a cellular response to an apoptogenic stimulus, where such response is an indicator of altered mitochondrial function as provided herein.

By way of background, mitochondrial dysfunction is thought to be critical in the cascade of events leading to apoptosis in various cell types (Kroemer et al., *FASEB J. 9*:1277-87, 1995). Altered mitochondrial physiology may be among the earliest events in programmed cell death (Zamzami et al., *J. Exp. Med. 182*:367-77, 1995; Zamzami et al., *J. Exp. Med. 181*:1661-72, 1995) and elevated reactive oxygen species (ROS) levels that result from such altered mitochondrial function may initiate the apoptotic cascade (Ausserer et al., *Mol. Cell. Biol. 14*:5032-42, 1994). In several cell types, reduction in the mitochondrial membrane potential ($\Delta\Psi m$) precedes the nuclear DNA degradation that accompanies apoptosis. In cell-free systems, mitochondrial, but not nuclear, enriched fractions are capable of inducing nuclear apoptosis (Newmeyer et al., *Cell 70*:353-64, 1994). Perturbation of mitochondrial respiratory activity leading to altered cellular metabolic states, such as elevated intracellular ROS, may occur in certain diseases associated with altered mitochondrial function (*e.g.*, type 2 DM) and may further induce pathogenetic events via apoptotic mechanisms.

Oxidatively stressed mitochondria may release a pre-formed soluble factor that can induce chromosomal condensation, an event preceding apoptosis (Marchetti et al., *Cancer Res. 56*:2033-38, 1996). In addition, members of the Bcl-2 family of anti-apoptosis gene products are located within the outer mitochondrial membrane (Monaghan et al., *J. Histochem. Cytochem. 40*:1819-25, 1992) and these proteins appear to protect membranes from oxidative stress (Korsmeyer et

al, *Biochim. Biophys. Act. 1271*:63, 1995). Localization of Bcl-2 to this membrane appears to be indispensable for modulation of apoptosis (Nguyen et al., *J. Biol. Chem. 269*:16521-24, 1994). Thus, changes in mitochondrial physiology may be important mediators of apoptosis.

Altered mitochondrial function, may therefore lower the threshold for induction of apoptosis by an apoptogen. A variety of apoptogens are known to those familiar with the art (see, *e.g.,* Green et al., 1998 *Science* 281:1309 and references cited therein) and may include by way of illustration and not limitation: tumor necrosis factor-alpha (TNF-α); Fas ligand; glutamate; N-methyl-D-aspartate (NMDA); interleukin-3 (IL-3); herbimycin A (Mancini et al., 1997 *J. Cell. Biol.* 138:449-469); paraquat (Costantini et al., 1995 *Toxicology* 99:1-2); ethylene glycols; protein kinase inhibitors, such as, *e.g.* staurosporine, calphostin C, caffeic acid phenethyl ester, chelerythrine chloride, genistein; 1-(5-isoquinolinesulfonyl)-2-methylpiperazine; N-[2-((*p*-bromocinnamyl)amino)ethyl]-5-5-isoquinolinesulfonamide; KN-93; quercitin; d-*erythro*-sphingosine derivatives; UV irradiation; ionophores such as, *e.g.*: ionomycin and valinomycin; MAP kinase inducers such as, *e.g.*: anisomycin, anandamine; cell cycle blockers such as, *e.g.*: aphidicolin, colcemid, 5-fluorouracil, homoharringtonine; acetylcholinesterase inhibitors such as, *e.g.* berberine; anti-estrogens such as, *e.g.*: tamoxifen; pro-oxidants, such as, *e.g.*,: tert-butyl peroxide, hydrogen peroxide; free radicals such as, *e.g.*, nitric oxide; inorganic metal ions, such as, *e.g.*, cadmium; DNA synthesis inhibitors such as, *e.g.*: actinomycin D; DNA intercalators such as, *e.g.*, doxorubicin, bleomycin sulfate, hydroxyurea, methotrexate, mitomycin C, camptothecin, daunorubicin; protein synthesis inhibitors such as, *e.g.*, cycloheximide, puromycin, rapamycin; agents that affect microtubulin formation or stability such as, *e.g.*: vinblastine, vincristine, colchicine, 4-hydroxyphenylretinamide, paclitaxel; Bad protein, Bid protein and Bax protein (see, *e.g.,* Jurgenmeier et al., 1998 *Proc. Nat. Acad. Sci. USA* 95:4997-5002 and references cited therein); calcium and inorganic phosphate (Kroemer et al., 1998 *Ann. Rev. Physiol. 60*:619).

In one embodiment of the subject invention method wherein the indicator of altered mitochondrial function is a cellular response to an apoptogen, cells in a biological sample that are suspected of undergoing apoptosis may be examined for morphological, permeability or other changes that are indicative of an apoptotic state. For example by way of illustration and not limitation, apoptosis in many cell types may cause altered morphological appearance such as plasma membrane blebbing, cell shape change, loss of substrate adhesion properties or other morphological changes that can be readily detected by a person having ordinary skill in the art, for example by using light microscopy. As another example, cells undergoing apoptosis may exhibit fragmentation and disintegration of chromosomes, which may be apparent by microscopy and/or through the use of DNA-specific or chromatin-specific dyes that are known in the art, including fluorescent dyes. Such cells may also exhibit altered plasma membrane permeability properties as may be readily detected through the use of vital dyes (*e.g.,* propidium iodide, trypan blue) or by the detection of lactate dehydrogenase leakage into the extracellular milieu. These and other means for detecting apoptotic cells by morphologic criteria, altered plasma membrane permeability and related changes will be apparent to those familiar with the art.

In another embodiment of the subject invention method wherein the indicator of altered mitochondrial function is a cellular response to an apoptogen, cells in a biological sample may be assayed for translocation of cell membrane phosphatidylserine (PS) from the inner to the outer leaflet of the plasma membrane, which may be detected, for example, by measuring outer leaflet binding by the PS-specific protein annexin. (Martin et al., *J. Exp. Med. 182*:1545, 1995; Fadok et al., *J. Immunol. 148*:2207, 1992.) In still another embodiment of this aspect of the invention, a cellular response to an apoptogen is determined by an assay for induction of specific protease activity in any member of a family of apoptosis-activated proteases known as the caspases (see, *e.g.,* Green et al., 1998 *Science* 281:1309). Those having ordinary skill in the art will be readily familiar with methods for determining caspase activity, for example by determination of caspase-mediated cleavage of specifically recognized protein

substrates. These substrates may include, for example, poly-(ADP-ribose) polymerase (PARP) or other naturally occurring or synthetic peptides and proteins cleaved by caspases that are known in the art (*see, e.g.,* Ellerby et al., 1997 *J. Neurosci. 17*:6165). The synthetic peptide Z-Tyr-Val-Ala-Asp-AFC (SEQ ID NO:__;), wherein "Z" indicates a benzoyl carbonyl moiety and AFC indicates 7-amino-4-trifluoromethylcoumarin (Kluck et al., 1997 *Science 275*:1132; Nicholson et al., 1995 *Nature 376*:37), is one such substrate. Other non-limiting examples of substrates include nuclear proteins such as U1-70 kDa and DNA-PKcs (Rosen and Casciola-Rosen, 1997 *J. Cell. Biochem. 64*:50; Cohen, 1997 *Biochem. J. 326*:1).

As described above, the mitochondrial inner membrane may exhibit highly selective and regulated permeability for many small solutes, but is impermeable to large (>~10 kDa) molecules. (*See, e.g.,* Quinn, 1976 *The Molecular Biology of Cell Membranes*, University Park Press, Baltimore, Maryland). In cells undergoing apoptosis, however, collapse of mitochondrial membrane potential may be accompanied by increased permeability permitting macromolecule diffusion across the mitochondrial membrane. Thus, in another embodiment of the subject invention method wherein the indicator of altered mitochondrial function is a cellular response to an apoptogen, detection of a mitochondrial protein, for example cytochrome c that has escaped from mitochondria in apoptotic cells, may provide evidence of a response to an apoptogen that can be readily determined. (Liu et al., *Cell 86*:147, 1996) Such detection of cytochrome c may be performed spectrophotometrically, immunochemically or by other well established methods for determining the presence of a specific protein.

For instance, release of cytochrome c from cells challenged with apoptotic stimuli (*e.g.,* ionomycin, a well known calcium ionophore) can be followed by a variety of immunological methods. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry coupled with affinity capture is particularly suitable for such analysis since apo-cytochrome c and holo-cytochrome c can be distinguished on the basis of their unique molecular weights. For example, the Surface-Enhanced Laser Desorption/Ionization (SELDI^{TM})

system (Ciphergen, Palo Alto, California) may be utilized to detect cytochrome c release from mitochondria in apoptogen treated cells. In this approach, a cytochrome c specific antibody immobilized on a solid support is used to capture released cytochrome c present in a soluble cell extract. The captured protein is then encased in a matrix of an energy absorption molecule (EAM) and is desorbed from the solid support surface using pulsed laser excitation. The molecular mass of the protein is determined by its time of flight to the detector of the SELDI™ mass spectrometer.

A person having ordinary skill in the art will readily appreciate that there may be other suitable techniques for quantifying apoptosis, and such techniques for purposes of determining an indicator of altered mitochondrial function that is a cellular response to an apoptogenic stimulus are within the scope of the methods provided by the present invention.

As noted above, an increasing number of diseases, disorders and conditions have been identified as diseases associated with altered mitochondrial function as provided herein, such that given the present disclosure and the state of the art with respect to methods for assessing mitochondrial function and with respect to clinical signs and symptoms of such diseases, the person having ordinary skill in the art can readily determine criteria for establishing a statistically significant deviation from a normal range for one or more parameters that are appropriate to the definition of the disease, in order to establish that a disease associated with altered mitochondrial function is present. As an illustrative example, where it is desirable to determine whether or not a subject or biological source falls within clinical parameters indicative of type 2 diabetes mellitus, signs and symptoms of type 2 diabetes that are accepted by those skilled in the art may be used to so designate a subject or biological source, for example clinical signs referred to in Gavin et al. (*Diabetes Care* 22(suppl. 1):S5-S19, 1999, American Diabetes Association Expert Committee on the Diagnosis and Classification of Diabetes Mellitus) and references cited therein, or other means known in the art for diagnosing type 2 diabetes. Similarly, those familiar with the art will be aware of

art accepted criteria for determining the presence of other diseases associated with altered mitochondrial function as provided herein.

Hence, the person having ordinary skill in the art can "correlate" one or more parameters described herein (*e.g.*, mitochondrial functions) with such a disease associated with altered mitochondrial function, in view of the present disclosure and based on familiarity with the art. Briefly, statistically significant deviation from a normal, disease-free range for any of a number of clinical signs and symptoms and/or criteria for mitochondrial function, permits determination of the statistically significant coincidence of such parameter(s) with disease. Such deviation can further be confirmed, for instance, by comparing the same parameters and criteria that are detected in disease to those in a suitable control sample, in this case a control derived from a subject known to be free of a risk for having, or presence of, such disease.

Accordingly, given the disclosure of the instant application, and in particular the identification of the polypeptide sequences set forth in SEQ ID NOS:1-3025 as belonging to a defined human mitochondrial proteome, the present invention provides a control set of polypeptides such that a sample may be analyzed for the presence of at least one modified polypeptide as described herein, in order to so "correlate" such modification with a disease associated with altered mitochondrial function. Establishing such a correlation then provides a target for screening assays to identify an agent suitable for therapeutic intervention, *i.e.*, an agent that beneficially counteracts the disease-associated alteration in mitochondrial function. Without wishing to be bound by theory, a target for therapeutic intervention preferably contributes to the pathogenesis of disease by exhibiting undesirably altered biological activity, such that a therapeutic agent reverses such alteration to a control range. The invention need not, however, be so limited, as even in situations where the target identified according to the subject invention method is a surrogate marker of disease, such a target nevertheless may be restored to a normal control range by a therapeutic agent regardless of whether the interaction is direct, in a manner that ameliorates disease. In certain embodiments the invention further provides for determination

of altered biological activity in such a modified polypeptide, as also described herein.

According to the present invention, there are provided compositions and methods for the identification of differential protein expression at the organellar proteome level (*e.g.*, the mitochondrial proteome), in a sub-proteomic, complex mixture of proteins or at the level of a single targeted protein. The invention thus relates in pertinent part to the unexpected advantages associated with the unique physicochemical properties of particular organelle-derived (*e.g.*, mitochondria) polypeptides, peptides (*e.g.*, peptide fragments) and proteins, in conjunction with biochemical (including immunochemical) methods, modern spectrometry and protein bioinformatics software tools to identify peptides and proteins that are detected as differentially expressed products, and to identify previously unrecognized peptides and proteins as molecular components of a particular organelle (*e.g.*, mitochondrial molecular components as provided herein).

The invention also relates in pertinent part to the surprising advantages offered by the use of an organelle enriched sample fraction (*e.g.*, a mitochondria enriched sample as provided herein). Determining the pattern of differential protein expression (*e.g.*, absence or presence of one or more particular proteins in a sample; structural modification of a particular protein; or other altered expression such as a statistically significant increase or decrease in the amount of one or more particular proteins in a sample when normalized to a control) at the peptide and/or protein level in a complex protein mixture obtained from a biological sample as provided herein (*i.e.*, at the proteomic level) provides, in certain embodiments, targets for drug screening assays and for therapeutic intervention in specific disease states. Accordingly, in certain embodiments the invention provides methods for evaluating the effects of candidate therapeutic agents (*e.g.*, drugs or biological stimuli as provided herein) on biological activity of a mitochondrial protein, for example, where the protein exhibits altered biological activity due to one or more of a modification such as a mutation (insertion, deletion and/or substitution of one or more amino acids), a posttranslational modification or an altered level of protein expression. Thus, in certain embodiments, such

candidate agents may cause one or more specific alterations (*e.g.,* increases or decreases in a statistically significant manner) in the biological activity of a mitochondrial protein , preferably in some beneficial fashion.

As also noted elsewhere herein, certain embodiments of the invention relate in pertinent part to isolating at least one mitochondrial polypeptide according to any of a variety of biochemical separation methodologies for isolating a polypeptide as known in the art and as provided herein (see, *e.g.,* Scopes, 1987 *Protein Purification: Principles and Practice*, Springer-Verlag, NY; Deutscher, 1990 *Meths. Enzymol.* Vol. 182; Nilsson et al., 2000 *Mass Spectrom. Rev.* 19:390; Godovac-Zimmermann et al., 2001 *Mass Spectrom. Rev.* 20:1; Gatlin et al., 2000 *Anal. Chem.* 72:757; Link et al., 1999 *Nat. Biotechnol.* 17:676). Hence, as provided herein and as known to the art, such methodologies for isolating a mitochondrial polypeptide may exploit physicochemical and hydrodynamic properties of the polypeptide, including, for example, the approximate apparent molecular mass of the polypeptide, the amino acid sequence of the polypeptide, and in certain contemplated embodiments, the apparent approximate isolelectric focusing point of the polypeptide.

As is well known to those having ordinary skill in the art, variability in biological sample source and condition, extraction reagents and methods, separation media and instrumentation, analytical apparatus and the like, may account for differences in values observed for such properties of polypeptides as molecular mass and isoelectric focusing point. Hence, it will be understood that an "apparent" molecular mass or isoelectric focusing point refers to that which is detected in a particular rendition of a particular isolation procedure, although the value detected for such a parameter may vary among separate isolations; similarly those familiar with the art will appreciate that from among the variables listed above, including imprecision in instrumentation, apparent values may vary in a manner that renders a particular value that is detected only an "approximation" of the actual parameter being measured. Thus, according to certain embodiments of the present invention a mitochondrial polypeptide may be isolated on the basis of approximate apparent molecular mass, apparent approximate isoelectric focusing

point and/or amino acid sequence, which parameters may be susceptible to some variability for reasons discussed above but which, in any event, will permit isolation of such a polypeptide as provided herein.

The isolated polypeptide is then contacted with a proteolytic agent to generate a plurality of derivative peptide fragments, from which a mass spectrum can be generated to permit determination of the presence, amount or structure (*e.g.,* level) of the polypeptide in the sample, which may then be compared to similarly obtained levels of a mitochondrial polypeptide obtained from other samples.

In an effort to better understand the molecular details of mitochondrial dysfunction as a contributing factor in disease, a high-resolution map of the human mitochondrial proteome is disclosed herein using human heart tissue as the source of isolated mitochondria, which are further enriched on metrizamide density gradients, solubilized and fractionated using sucrose density gradients. Although a protein map was previously generated using an only partially enriched mitochondrial fraction from human placenta (Rabilloud et al., 1998 *Electrophor.* 19:1006), no reliable database cataloguing mitochondrial proteins is currently available (*cf.*, *e.g.*, Koc et al., 2000 *J. Biol. Chem.* 275:32585; Lopez et al., 2000 *Electrophor.* 21:3427). Typically, mitochondria may be obtained from brain, heart, skeletal muscle or liver, where they are most abundant, although other sources (*e.g.,* blood platelets) may also be used. According to the present invention there is provided a framework for investigating mitochondrial proteins, including identifying previously unrecognized mitochondrial proteins (*e.g.,* novel proteins or known proteins not previously known to exist as mitochondrial molecular components) as well as those that are modified as provided herein as a correlate of disease, by mapping the human heart mitochondrial proteome. As described in greater detail in the Examples, mitochondrial proteins in distinct sucrose density gradient fractions were separated by one-dimensional polyacrylamide gel electrophoresis, and isolated proteins recovered from gels were analyzed as described below using matrix assisted laser desorption ionization (MALDI) and MALDI-post source decay (MALDI-PSD) techniques. (For other MS methods for

proteins, see, *e.g.,* Godovac-Zimmermann et al., 2001 *Mass Spectromet. Rev.* 20:1-57; Nilsson et al., 2000 *Mass Spectromet. Rev.* 19:390-397.) Over 1400 proteins were identified in the NCBI (http://www.ncbi.nlm.nih.gov/Entrez/) and GenPept (http://www.ncbi.nlm.nih.gov/ Entrez/ protein.html) databases. Alternative databases for identifying protein sequences are known to the art and include, for example, Swissprot (http://www.expasy.ch/sprot/sprot-top.html), and owl (http://www.biochem.ucl .ac.uk/bsm/dbbrowser/OWL/OWL.html.) The data set so obtained provides for the identification of proteins present in mitochondria from human heart, a bioenergetically active tissue.

As described in greater detail below, the present invention is also directed in pertinent part to the use of mass spectrometry (MS), and in particular to the use of matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry, for the analysis of mitochondrial proteins and peptides obtained from a subject or biological source as provided herein.

In particularly preferred embodiments of the present invention, all or a portion of a protein fraction derived from a biological sample as provided herein may be contacted with one or more proteolytic agents under conditions and for a time sufficient to generate a plurality of peptide fragments derived from the protein fraction. Peptide fragments are typically continuous portions of a polypeptide chain derived from a protein of the protein fraction, which portions may be up to about 100 amino acids in length, preferably up to about 50 amino acids in length, more preferably up to about 30 amino acids in length, and still more preferably up to about 15-20 amino acids in length. In particularly preferred embodiments peptide fragments are 10-15 amino acids in length, and in other preferred embodiments peptide fragments may be 2-12 amino acids long.

A variety of proteolytic agents and suitable conditions for using them are known in the art, any of which may be useful according to certain embodiments of the present invention wherein peptide fragments are generated. Particularly preferred are proteolytic agents that are proteolytic enzymes or proteases, for example trypsin, Glu-C protease (*Staphylococcal* V8 protease), Lys-C protease, Arg-C protease, or other proteases known in the art to cleave peptides at specific

amino acid linkages, typically at a relatively limited number of cleavage sites within a protein or polypeptide. Other useful proteolytic agents that are proteolytic enzymes include serine proteases, for example, chymotrypsin, elastase and trypsin; thiol proteases, such as papain or yeast proteinase B; acid proteases, including, *e.g.,* pepsin or cathepsin D; metalloproteinases *(e.g.,* collagenases, microbial neutral proteinases); carboxypeptidases; N-terminal peptidases or any other proteolytic enzymes that those having ordinary skill in the art will recognize may be employed to generate peptide fragments as provided herein (see, *e.g.,* Bell, J.E. and Bell, E.T., *Proteins and Enzymes*, 1988 Prentice-Hall, Englewood Cliffs, NJ; *Worthington Enzyme Manual*, V. Worthington, ed., 1993 Worthington Biochemical Corp., Freehold, NJ).

Alternatively, in certain embodiments it may be desirable to use proteolytic agents that are chemical agents, for example HCl, CNBr, formic acid, N-bromosuccinimide, BNPS-skatole, *o*-iodosobenzoic acid/ *p*-cresol, Cyssor, 2-nitro-5-thiocyanobenzoic acid, hydroxylamine, pyridine/ acetic acid or other chemical cleavage procedures (see, *e.g.,* Bell and Bell, 1988, and references cited therein).

As noted above, oxidative damage to proteins, such as protein modification that results from reactive free radical activity in biological systems, is an underlying feature in the pathogenesis of a number of diseases. Accordingly, a disease associated with altered mitochondrial function, for example a disease associated with altered mitochondrial constitution or composition (*e.g.,* a disorder or condition characterized by statistically significant alterations in the quantity, structure and/or activity of one or more mitochondrial molecular components as provided herein) may also include a "disease associated with oxidative modification of a protein", such as any disease in which at least one protein or peptide is oxidatively (*e.g.,* covalently) and, in most cases, inappropriately modified. In highly preferred embodiments, at least one protein or peptide in a subject or biological source having a disease associated with oxidative modification of a protein includes a mitochondrial protein that has undergone disease-associated oxidative damage. Thus, such a disease may have a basis in

a respiratory or metabolic or other defect, whether mitochondrial or extramitochondrial in origin. Diseases associated with oxidative modification of proteins may include Alzheimer's disease (AD), diabetes mellitus, Parkinson's disease, amyotrophic lateral sclerosis (ALS), atherosclerosis and other degenerative and inflammatory diseases. Those familiar with the art will be aware of clinical criteria for diagnosing certain of these diseases, which diagnostic criteria are augmented in view of the subject invention methods and compositions.

As described in greater detail in the Examples, certain embodiments of the invention contemplate the unexpected discovery that a mitochondrial protein or peptide containing tryptophan may be oxidatively modified to yield proteins or peptides containing this modified amino acid, although the invention is not intended to be so limited and as described herein contemplates mitochondrial proteins and peptides comprising a wide variety of other amino acids that may be oxidatively modified, according to oxidation reactions such as those described, for example, in Halliwell and Gutteridge (*Free Radicals in Biology and Medicine*, 1989 Clarendon Press, Oxford, UK). As described below, a number of mitochondrial proteins have been identified in which at least one tryptophan residue was doubly oxidized, thereby undergoing conversion to N-formylkynurenine. Accordingly, in certain embodiments the invention contemplates determination of a modified polypeptide (*e.g.*, SEQ ID NOS:1-3025) comprising an oxidative modification that may, in certain further embodiments comprise an oxidized trytophan residue, which may in certain still further comprise N-formylkynurenine. Identification and determination of oxidative modification of tryptophan in proteins and peptides are well known to those familiar with the art (*e.g.*, Halliwell and Gutteridge, pages 93-97; 315-320; 413-429).

For instance, the oxidation of tryptophan to N-formylkynurenine in proteins has been known for over 35 years since Previero et al. described it in hen's egg-white lysozyme in anhydrous formic acid (1967 *J. Mol. Biol.* 24:261). Kuroda et al. (1975 *J. Biochem. (Tokyo)* 78:641) subsequently found inactivation of lysozyme by ozone in aqueous solution occurred only when one critical tryptophan residue was oxidized, thus providing the first evidence that oxidation of a specific

tryptophan residue can impair enzyme function. These early reports relied on identification of the tryptophan oxidation products by characteristic electronic absorption spectra. Finley et al. (1998 *Protein Sci.* 7:2391) exposed α-crystallin from bovine lens tissue to Fenton chemistry *in vitro* and separated the component tryptic peptides by HPLC. Tandem MS/MS spectrometry was used to identify oxidized amino acid sites by +16, +32 and +4 u increases in the molecular mass of peptide fragment ions containing tryptophan residues. Structures corresponding to those mass shifts are shown in Fig. 3. More recently Thiede et al. (2000 *Rapid Commun. Mass Spectrom.* 14:496) described oxidatively modified tryptophan residues in peptides from human Jurkat T lymphoblastoid cells. These workers described oxidatively modified tryptophan in a peptide which, as shown by the Examples provided herein, shares structure with a similar peptide derived from the mitochondrial voltage dependent anion channel-1 (VDAC1, *e.g.*, SEQ ID NO:2559) polypeptide (see Table 3, KLETAVNLAWTAGNSNTR). Certain embodiments of the present invention therefore contemplate expressly excluding determination of the peptide KLETAVNLAWTAGNSNTR which comprises oxidatively modified tryptophan, certain other embodiments contemplate expressly excluding an oxidatively modified VDAC1 polypeptide, and certain other embodiments of the present invention therefore contemplate expressly excluding a disease associated with altered mitochondrial function that is T-cell lymphoma or leukemia.

In order to determine whether a mitochondrial component may contribute to a particular disease associated with oxidative modification of a protein, it may be useful to construct a model system for diagnostic tests and for screening candidate therapeutic agents in which the nuclear genetic background may be held constant while the mitochondrial genome is modified. It is known in the art to deplete mitochondrial DNA from cultured cells to produce ρ^0 cells, thereby preventing expression and replication of mitochondrial genes and inactivating mitochondrial function. It is further known in the art to repopulate such ρ^0 cells with mitochondria derived from foreign cells in order to assess the contribution of the donor mitochondrial genotype to the respiratory phenotype of the recipient cells. Such cytoplasmic hybrid cells, containing genomic and

mitochondrial DNAs of differing biological origins, are known as cybrids. See, for example, International Publication Number WO 95/26973 and U.S. Patent No. 5,888,498 which are hereby incorporated by reference in their entireties, and references cited therein.

According to the present invention, a level of at least one mitochondrial protein or peptide is determined in a biological sample from a subject or biological source. For subjects that are asymptomatic, that exhibit a pre-disease phenotype or that meet clinical criteria for having or being at risk for having a particular disease, such determination may have prognostic and/or diagnostic usefulness. For example, where other clinical indicators of a given disease are known, levels of at least one mitochondrial protein or peptide in subjects known to be free of a risk or presence of such disease based on the absence of these indicators may be determined to establish a control range for such level(s). The levels may also be determined in biological samples obtained from subjects suspected of having or being at risk for having the disease, and compared to the control range determined in disease free subjects. Those having familiarity with the art will appreciate that there may be any number of variations on the particular subjects, biological sources and bases for comparing levels of at least one mitochondrial protein or peptide that are useful beyond those that are expressly presented herein, and these additional uses are within the scope and spirit of the invention.

For instance, determination of levels of at least one mitochondrial protein or peptide may take the form of a prognostic or a diagnostic assay performed on a skeletal muscle biopsy, on whole blood collected from a subject by routine venous blood draw, on buffy coat cells prepared from blood or on biological samples that are other cells, organs or tissue from a subject. Alternatively, in certain situations it may be desirable to construct cybrid cell lines using mitochondria from either control subjects or subjects suspected of being at risk for a particular disease associated with oxidative modification of proteins. Such cybrids may be used to determine levels of at least one mitochondrial peptide or protein for diagnostic or predictive purposes, or as biological sources for screening

assays to identify agents that may be suitable for treating the disease based on their ability to alter (*e.g.,* to increase or decrease in a statistically significant manner) the levels of at least one mitochondrial protein or peptide in treated cells.

In one embodiment of this aspect of the invention, therapeutic agents or combinations of agents that are tailored to effectively treat an individual patient's particular disease may be identified by routine screening of candidate agents on cybrid cells constructed with the patient's mitochondria. In another embodiment, a method for identifying subtypes of the particular disease is provided, for example, based on differential effects of individual candidate agents on cybrid cells constructed using mitochondria from different subjects diagnosed with the same disease.

MALDI

As noted above, in certain preferred embodiments of the present invention there is provided a method for identifying at least one mitochondrial protein comprising generating a mass spectrum of a mitochondrial polypeptide-derived peptide fragment, wherein the mass spectrum is preferably generated using MALDI-TOF. By way of background, in 1987, matrix-assisted laser desorption/ionization mass spectrometry (MALDI) was introduced by Hillenkamp and Karas, and since has become a very powerful bioanalytical tool (*Anal. Chem. 60*:2288-2301, 1988; *see also* Burlingame et al., *Anal. Chem. 68*:599-651, 1996 and references cited therein). The success of MALDI in the area of protein science can be attributed to several factors. The greatest of these is that MALDI can be rapidly (~5 minutes) applied as an analytical technique to analyze small quantities of virtually any protein (practical sensitivities of ~ 1 pmole protein loaded into the mass spectrometer). The technique is also extremely accurate. Beavis and Chait demonstrated that the molecular weights of peptides and proteins can be determined to within ~ 0.01% by using methods in which internal mass calibrants (x-axis calibration) are introduced into the analysis (*Anal. Chem. 62*:1836-40, 1990). MALDI can also be made quantitative using a similar method in which internal reference standards are introduced into the analysis for ion signal

normalization (y-axis calibration). Quantitative determination of proteins and peptides is possible using this approach with accuracies on the order of ~ 10 % (Nelson et al., *Anal. Chem.* 66:1408-15, 1994). Finally, MALDI is extremely tolerant of large molar excesses of buffer salts and, more importantly, the presence of other proteins.

With the high tolerance towards buffer salts and other biomolecular components comes the ability to directly analyze complex biological mixtures. Many examples exist where MALDI is used to directly analyze the results of proteolytic or chemical digestion of polypeptides (*see* Burlingame et al., *supra*). Other examples extend to elucidating post-translational modifications (namely carbohydrate type and content), a process requiring the simultaneous analysis of components present in a heterogeneous glycoprotein mixture (Sutton et al., *Techniques in Protein Chemistry III*, Angeletti, Ed., Academic Press, Inc., New York, pp. 109-116, 1993). Arguably, the most impressive use of direct mixture analysis is the screening of natural biological fluids. In that application, proteins are identified, as prepared directly from the host fluid, by detection at precise and characteristic mass-to-charge (*m/z*) values (Tempst et al., *Mass Spectrometry in the Biological Sciences*, Burlingame and Carr, Ed., Humana Press, Totowa, NJ, p.105, 1996).

The use of an affinity ligand-derivatized support to selectively retrieve a target analyte specifically for MALDI analysis was first demonstrated by Hutchens and Yip (*Rapid Commun. Mass Spectrom.* 7:576-80, 1993). Those investigators used single-stranded DNA-derivatized agarose beads to selectively retrieve a protein, lactoferrin, from pre-term infant urine by incubating the beads with urine. The agarose beads were then treated as the MALDI analyte – a process involving mixing with a solution-phase MALDI matrix followed by deposition of the mixture on a mass spectrometer probe. MALDI then proceeded in the usual manner. Results indicated that the derivatized beads selectively retrieved and concentrated the lactoferrin; enough so to enable ion signal in the MALDI mass spectrum adequate to unambiguously identify the analyte at the appropriate m/z value (81,000 Da). A number of variations on this approach have

since been reported. These include the use of immunoaffinity precipitation for the MALDI analysis of transferrins in serum (Nakanishi et al., *Biol. Mass Spectrom.* *23*:230-33, 1994), screening of ascites for the production of monoclonal antibodies (Papac et al., *Anal. Chem.* *66*:2609-13, 1994), and the identification of linear epitope regions within an antigen (Zhao et al., *Anal. Chem.* *66*:3723-26, 1994). Even more recently, the affinity capture approaches have been made rigorously quantitative by incorporating mass-shifted variants of the analyte into the analysis (Nelson et al. *Anal. Chem.* *67*:1153-58, 1995). The variants are retained throughout the analysis (in the same manner as the true analyte) and observed as unique (resolved) signals in the MALDI mass spectrum. Quantification of the analyte is performed by equating the relative ion signals of the analyte and variant to an analyte concentration.

Suitable mass spectrometers include, but are not limited to, a magnetic sector mass spectrometer, a Fourier transform ion cyclotron resonance (FTICR) mass spectrometer, a quadrupole (rods or ion trap) mass spectrometer and a time-of-flight (TOF) mass spectrometer, and/or various hybrid instruments comprising combinations of any two or more of such types of mass analyzer (*e.g.,* quadrupole/ orthogonal TOF, Qq/TOF, TOF/TOF, etc.). In a preferred embodiment, the mass spectrometer is a time TOF mass spectrometer.

Since large molecules, such as peptides and proteins, are generally too large to be desorbed/ionized intact, a matrix is used to assist laser desorption/ionization of the same. This technique is referred to as matrix assisted laser desorption/ionization or (MALDI), and the matrix agent is referred to as a "MALDI matrix." In short, the analyte is contacted with a suitable MALDI matrix and allowed to crystallize. Suitable MALDI matrix materials are known to those skilled in this field, and include, for example, derivatives of cinnamic acid such as α-cyano-4-hydroxycinnamic acid (ACCA) and sinapinic acid (SA).

A first criterion to performing mass spectrometry on the analyte captured by the interactive surface is the generation of vapor-phase ions. In the practice of this invention, such species are generated by desorption/ionization techniques. Suitable techniques include desorption/ionization methods derived

from impact of particles with the sample. These methods include fast atom bombardment (FAB – impact of neutrals with a sample suspended in a volatile matrix), secondary ion mass spectrometry (SIMS – impact of keV primary ions generating secondary ions from a surface), liquid SIMS (LSIMS – like FAB except the primary species is an ion), plasma desorption mass spectrometry (like SIMS except using MeV primary ions), massive cluster impact (MCI – like SIMS using large cluster primary ions), laser desorption/ionization (LDI – laser light is used to desorb/ionize species from a surface), and matrix-assisted laser desorption/ionization (MALDI – like LDI except the species are desorbed/ionized from a matrix capable of assisting in the desorption and ionization events). Any of the aforementioned desorption/ionization techniques may be employed in the practice of the present invention. In a preferred embodiment, LDI is employed, and in a more preferred embodiment, MALDI is utilized. For matrix assisted laser desorption ionization/ time of flight (MALDI-TOF) analysis or other MS (mass spectrometry) techniques known to those skilled in the art, see, for example, U.S. Patent Nos. 5,622,824, 5,605,798 and 5,547,835. Alternatively, other soft-ionization mechanisms that are not based on particle bombardment but that are also capable of ionizing peptides and/or proteins could be employed. Such methods include electrospray ionization (ESI, liquid flow containing analyte sprayed from a nozzle or needle at high voltage) or atmospheric pressure ionzation (API).

SCREENING ASSAYS AND AGENTS

In certain embodiments, the present invention provides a method of identifying an agent for treating a disease associated with altered mitochondrial function, comprising (a) contacting a candidate agent with a biological sample from a subject having a disease associated with altered mitochondrial function, wherein the sample comprises at least one polypeptide that exhibits altered biological activity which accompanies the disease and wherein the polypeptide is (i) a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1- 3025, or (ii) a modified polypeptide that comprises at least one

modification to a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1- 3025; and (b) determining an increase or decrease in the altered biological activity of the polypeptide in the presence of the candidate agent relative to the level of the altered biological activity in the absence of the candidate agent, and therefrom identifying an agent for treating a disease associated with altered mitochondrial function.

Candidate agents for use in these and related methods of screening for a modulator of mitochondrial protein or peptide according to the present invention may be provided as "libraries" or collections of compounds, compositions or molecules. Such molecules typically include compounds known in the art as "small molecules" and having molecular weights less than 10^5 daltons, preferably less than 10^4 daltons and still more preferably less than 10^3 daltons. For example, members of a library of test compounds can be administered to a plurality of samples, and then assayed for their ability to increase or decrease the level of at least one indicator of altered mitochondrial function.

Candidate agents further may be provided as members of a combinatorial library, which preferably includes synthetic agents prepared according to a plurality of predetermined chemical reactions performed in a plurality of reaction vessels. For example, various starting compounds may be prepared employing one or more of solid-phase synthesis, recorded random mix methodologies and recorded reaction split techniques that permit a given constituent to traceably undergo a plurality of permutations and/or combinations of reaction conditions. The resulting products comprise a library that can be screened followed by iterative selection and synthesis procedures, such as a synthetic combinatorial library of peptides (see *e.g.,* PCT/US91/08694, PCT/US91/04666, which are hereby incorporated by reference in their entireties) or other compositions that may include small molecules as provided herein (see *e.g.,* PCT/US94/08542, EP 0774464, U.S. 5,798,035, U.S. 5,789,172, U.S. 5,751,629, which are hereby incorporated by reference in their entireties). Those having ordinary skill in the art will appreciate that a diverse assortment of such libraries may be prepared according to established procedures, and tested for their

influence on an indicator of altered mitochondrial function, according to the present disclosure.

The present invention provides compositions and methods that are useful in pharmacogenomics, for the classification and/or stratification of a subject or patient population. In one embodiment, for example, such stratification may be achieved by identification in a subject or patient population of one or more distinct profiles of at least one mitochondrial protein or peptide that is modified (*e.g.*, an altered expression level, altered amino acid sequence, altered posttranslational modification or an oxidative modification) or in which the biological activity is altered and that correlates with a particular disease associated with altered mitochondrial function. Such profiles may define parameters indicative of a subject's predisposition to develop the particular disease, and may further be useful in the identification of novel subtypes of that disease. In another embodiment, correlation of one or more traits in a subject with at least one mitochondrial protein or peptide (*e.g.*, expression levels of a mitochondrial protein that can be determined to differ from a control in a statistically significant manner) may be used to gauge the subject's responsiveness to, or the efficacy of, a particular therapeutic treatment. Similarly, where levels of at least one indicator mitochondrial protein or peptide and risk for a particular disease associated with altered mitochondrial function are correlated, the present invention provides advantageous methods for identifying agents suitable for treating such disease(s), where such agents affect levels of at least one mitochondrial protein or peptide (or levels of a modification) in a biological source. Such suitable agents will be those that alter (*e.g.*, increase or decrease) the level of at least one mitochondrial protein or peptide in a statistically significant manner. In certain preferred embodiments, a suitable agent alters a mitochondrial protein or peptide level in a manner that confers a clinical benefit, and in certain other, non-exclusive preferred embodiments, a suitable agent alters a mitochondrial protein or peptide level by causing it to return to a level detected in control or normal (*e.g.*, disease-free) subjects.

As described herein, determination of levels of at least one mitochondrial protein or peptide may also be used to stratify a patient population (*i.e.,* a population classified as having one or more diseases associated with altered mitochondrial function, for example, by oxidative modification of a protein). Accordingly, in another preferred embodiment of the invention, determination of levels of a mitochondrial protein or peptide in at least one protein or peptide in a biological sample from an oxidatively stressed subject may provide a useful correlative indicator for that subject. A subject so classified on the basis of mitochondrial protein expression levels may be monitored using any known clinical parameters for a specific disease referred to above, such that correlation between levels of at least one mitochondrial protein or peptide and any particular clinical score used to evaluate a particular disease may be monitored. For example, stratification of an AD patient population according to levels of at least one mitochondrial protein or peptide may provide a useful marker with which to correlate the efficacy of any candidate therapeutic agent being used in AD subjects.

In certain other embodiments, the invention provides a method of treating a patient having a disease associated with altered mitochondrial function by administering to the patient an agent that that compensates for at least one biological activity of a polypeptide that exhibits altered biological activity which accompanies the disease, wherein the polypeptide is (i) a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1-3025, or (ii) a modified polypeptide that comprises at least one modification to a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1-3025. As known to the art, an agent that "compensates" for an altered biological activity of a polypeptide includes an agent that counterbalances any structural or functional defect or alteration in such polypeptide, such as an altered biological activity arising as the result of a modification as provided herein, where such counterbalancing may be partial or full restoration of normal activity, or restoration to supranormal levels, so long as an effect is demonstrable in a statistically significant manner. In certain preferred embodiments the agent substantially

restores at least one mitochondrial protein or peptide to a level found in control or normal subjects (which in some cases may be an undetectable level). In a most preferred embodiment, an agent that substantially restores (*e.g.,* increases or decreases) at least one mitochondrial protein or peptide to a normal level effects the return of the level of that indicator to a level found in control subjects. In another preferred embodiment, the agent that substantially restores such an indicator confers a clinically beneficial effect on the subject. In another embodiment, the agent that substantially restores the indicator promotes a statistically significant change in the level of at least one mitochondrial protein or peptide. As noted herein, those having ordinary skill in the art can readily determine whether a change in the level of a particular mitochondrial protein or peptide brings that level closer to a normal value and/or clinically benefits the subject, based on the present disclosure. Thus, an agent that substantially restores at least one mitochondrial protein or peptide to a normal level may include an agent capable of fully or partially restoring such level. These and related advantages will be appreciated by those familiar with the art.

Any of the agents for treating a disease associated with altered mitochondrial function (*e.g.,* oxidative modification of a protein), identified as described herein, are preferably part of a pharmaceutical composition when used in the methods of the present invention. The pharmaceutical composition will include at least one of a pharmaceutically acceptable carrier, diluent or excipient, in addition to one or more agents for treating a disease associated with oxidative modification of a protein, and, optionally, other components.

"Pharmaceutically acceptable carriers" for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remingtons Pharmaceutical Sciences, Mack Publishing Co. (A.R. Gennaro edit. 1985). For example, sterile saline and phosphate-buffered saline at physiological pH may be used. Preservatives, stabilizers, dyes and even flavoring agents may be provided in the pharmaceutical composition. For example, sodium benzoate, sorbic acid and esters of *p*-hydroxybenzoic acid may be added as preservatives. *Id.* at 1449. In addition, antioxidants and suspending agents may be used. *Id.*

"Pharmaceutically acceptable salt" refers to salts of the compounds of the present invention derived from the combination of such compounds and an organic or inorganic acid (acid addition salts) or an organic or inorganic base (base addition salts). The compounds of the present invention may be used in either the free base or salt forms, with both forms being considered as being within the scope of the present invention.

The pharmaceutical compositions that contain one or more agents for treating a disease associated with oxidative modification of a protein may be in any form which allows for the composition to be administered to a patient. For example, the composition may be in the form of a solid, liquid or gas (aerosol). Typical routes of administration include, without limitation, oral, topical, parenteral (*e.g.*, sublingually or buccally), sublingual, rectal, vaginal, intrathecal and intranasal. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal, intracavernous, intrameatal, intraurethral injection or infusion techniques. The pharmaceutical composition is formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the composition to a patient. Compositions that will be administered to a patient take the form of one or more dosage units, where for example, a tablet may be a single dosage unit, and a container of one or more compounds of the invention in aerosol form may hold a plurality of dosage units.

For oral administration, an excipient and/or binder may be present. Examples are sucrose, kaolin, glycerin, starch dextrins, sodium alginate, carboxymethylcellulose and ethyl cellulose. Coloring and/or flavoring agents may be present. A coating shell may be employed.

The composition may be in the form of a liquid, *e.g.*, an elixir, syrup, solution, emulsion or suspension. The liquid may be for oral administration or for delivery by injection, as two examples. When intended for oral administration, preferred compositions contain, in addition to one or more agents for treating a disease associated with oxidative modification of a protein, one or more of a sweetening agent, preservatives, dye/colorant and flavor enhancer. In a composition intended to be administered by injection, one or more of a surfactant,

preservative, wetting agent, dispersing agent, suspending agent, buffer, stabilizer and isotonic agent may be included.

A liquid pharmaceutical composition as used herein, whether in the form of a solution, suspension or other like form, may include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or digylcerides which may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Physiological saline is a preferred adjuvant. An injectable pharmaceutical composition is preferably sterile.

A liquid composition intended for either parenteral or oral administration should contain an amount of agent(s) for treating a disease associated with oxidative modification of a protein such that a suitable dosage will be obtained. Typically, this amount is at least 0.01 wt% of an agent for treating a disease associated with oxidative modification of a protein in the composition. When intended for oral administration, this amount may be varied to be between 0.1 and about 70% of the weight of the composition. Preferred oral compositions contain between about 4% and about 50% of the agent for treating a disease associated with oxidative modification of a protein. Preferred compositions and preparations are prepared so that a parenteral dosage unit contains between 0.01 to 1% by weight of active compound.

The pharmaceutical composition may be intended for topical administration, in which case the carrier may suitably comprise a solution, emulsion, ointment or gel base. The base, for example, may comprise one or more of the following: petrolatum, lanolin, polyethylene glycols, beeswax, mineral oil, diluents such as water and alcohol, and emulsifiers and stabilizers. Thickening

agents may be present in a pharmaceutical composition for topical administration. If intended for transdermal administration, the composition may include a transdermal patch or iontophoresis device. Topical formulations may contain a concentration of the agent(s) for treating a disease associated with oxidative modification of a protein of from about 0.1 to about 10% w/v (weight per unit volume).

The composition may be intended for rectal administration, in the form, *e.g.*, of a suppository which will melt in the rectum and release the drug. The composition for rectal administration may contain an oleaginous base as a suitable nonirritating excipient. Such bases include, without limitation, lanolin, cocoa butter and polyethylene glycol.

In the methods of the invention, the agent(s) for treating a disease associated with oxidative modification of a protein may be administered through use of insert(s), bead(s), timed-release formulation(s), patch(es) or fast-release formulation(s).

It will be evident to those of ordinary skill in the art that the optimal dosage of the agent(s) for treating a disease associated with oxidative modification of a protein may depend on the weight and physical condition of the patient; on the severity and longevity of the physical condition being treated; on the particular form of the active ingredient, the manner of administration and the composition employed. It is to be understood that use of an agent for treating a disease associated with oxidative modification of a protein in a chemotherapy can involve such a compound being bound to an agent, for example, a monoclonal or polyclonal antibody, a protein or a liposome, which assist the delivery of said compound.

These and related advantages will be appreciated by those familiar with the art. The following Examples are offered by way of illustration and not limitation.

EXAMPLES

EXAMPLE 1

PREPARATION OF HUMAN HEART MITOCHONDRIA

Human heart mitochondria were obtained from Analytical Biological Services (Wilmington, DE) and were further purified by metrizamide gradient centrifugation (see, *e.g.,* Rosenthal, R.E., et al., 1987, *J. Cereb. Blood Flow Metab.* 7:752-8). Mitochondria (40 mg) were resuspended in MSHE (210 mM mannitol, 70 mM sucrose, 5 mM Hepes, 1 mM EGTA plus a Complete protease inhibitor cocktail tablet (Roche, Indianapolis, IN)) and loaded onto a 35%/17% metrizamide gradient in 6% Percoll. Gradients were centrifuged for 45 min at 19000 rpm, 4°C in a SW40 rotor. The heavy mitochondrial fraction was collected from the 35/17% interface, diluted in MSHE before pelleting at 12000 g for 10 min, and resuspended in MSHE. Protein concentrations were determined using the BioRad DC protein assay (BioRad Laboratories, Hercules, CA). The purity of the mitochondria was assessed by Western analysis using antisera directed against actin (Abcam, Cambridge, UK), dynamin II (Transduction Labs, Lexington, KY), KDEL, and LAMP1 (Stressgen, Victoria, BC Canada) to detect contamination due to cytoplasm, plasma membrane, ER, and lysosomes, respectively. The integrity of the mitochondria was assessed by Western analysis using a cocktail of antibodies directed against components of the electron transport chain; NDUFS2, 70 kD subunit of complex II, core I of complex III, cox 4, and ATP synthase alpha; all from Molecular Probes (Eugene, OR). A representative example of western immunoblot analysis of mitochondrial fractions prepared essentially as described here is shown in Figure 1.

EXAMPLE 2

SUCROSE DENSITY GRADIENT FRACTIONATION OF SOLUBILIZED MITOCHONDRIA

Metrizamide purified mitochondria (13 mg) were resuspended in MSHE plus protease inhibitors and solubilized with 1% lauryl maltoside for 25 min on ice with frequent vortexing. Samples were centrifuged at 14000 rpm, 4°C for 20 min. The pellet was frozen by immersion in liquid nitrogen and stored at -80°C. The supernatant was subjected to sucrose gradient centrifugation (Hanson, B.J. et al., 2001, *Electrophoresis* 22:950-959). The gradient consisted of 1 mL step-fractions of 35, 32.5, 30, 27.5, 25, 22.5, 20, 17.5, 15 and 10% sucrose in 10 mM Tris, pH 7.5/1 mM EDTA/0.05% lauryl maltoside, plus protease inhibitors). The solubilized mitochondria were loaded onto the gradient in 5% sucrose and centrifuged at 38000 rpm, 4°C for 16.5 h in a SW40 rotor. The gradient was collected from the bottom in 1 mL fractions. The gradient fractions were concentrated in Microcon YM-3 centrifugal concentrators (Millipore, Bedford, MA). The concentrated samples were quantitated using the BioRad DC protein reagent, snap frozen by immersion in liquid nitrogen and stored at -80°C. Separation of proteins across the gradient was initially assessed by subjecting 1□L aliquots of the concentrated fractions to electrophoresis on precast 4-12% NuPAGE gels in Mes buffer (Invitrogen, Carlsbad, CA) followed by staining with SimplyBlue Safe Stain (Invitrogen) or Western analysis using the cocktail of antibodies directed against components of the electron transport chain. Quantification of the electron transport chain complexes across the gradient was performed on images captured on a Fluor-S MultiImager (BioRad, Hercules, CA) and analyzed using QuantityOne software (BioRad).

Immediately prior to processing and analysis by mass spectrometry (see below), the concentrated gradient fractions and the solubilized pellet were successively subjected to electrophoresis on NuPAGE gels using ultraclean reagents. Buffers were made using HPLC grade water, and a gel rig and staining box were set aside for these samples. Aliquots (25 μg) of each concentrated

gradient fraction were loaded on a 4-12% NuPage gel and run at 25 mA for1 h, then 35 mA for another 1 h 20 min. Gels were fixed for 10 min (40% methanol, 10% acetic acid), washed three times for 5 min in HPLC grade water, stained with colloidal Coomassie for 10-15 sec, and then partially destained in water.

EXAMPLE 3

GEL PROCESSING AND MASS SPECTROMETRIC ANALYSIS OF POLYPEPTIDES

The lightly Coomassie-stained electrophoretic gels from Example 2 were imaged placed on a light box in a laminar flow hood on a plastic cutting mat with a 65 × 1mm grid placed underneath. To avoid keratin contamination all manipulations were performed wearing latex gloves, shower caps and lab coats. Starting at the bottom the gel, approximately 1mm slices were excised across the entire width of a gel lane with a clean razor, further cut into approximately 1 mm cubes and transferred to 500 μL microcentrifuge tubes that had been prewashed with 50:50 water: acetonitrile. This procedure was progressively continued to the top the gel to ensure comprehensive coverage of all proteins in the gel lane. Although most gel slices were 1mm thick, when discrete bands were encountered they were selectively excised, while near the top of the gel slightly thicker slices were taken where the protein concentration was lower. This resulted in 50-64 slices for each of the 12 lanes processed (corresponding to sucrose fractions 1-10, combined 11/12 and the pellet).

The gel pieces were incubated with 200 μL destain solution (25 mM ammonium bicarbonate, 25% acetonitrile) at 37°C for 45min. The destain solution was decanted and another cycle of destaining performed if there was residual coloration. The gel pieces were then dried on a Genevac concentrator using the "cool heat" setting (about 30 min). The dried gel pieces were slightly moistened with 5 μL 50 mM ammonium bicarbonate, 5% acetonitrile and 5 μL of freshly prepared ice cold Promega modified trypsin (0.1 mg/mL in 50 mM ammonium bicarbonate, 5% acetonitrile) added. The gel pieces were allowed to soak up the

trypsin solution for 10 min, and then were fully reswelled with a 65 μL aliquot of 50 mM ammonium bicarbonate, 5% acetonitrile. After an overnight incubation at 37°C, the digestion was terminated by addition of 7.5 μL 10% acetic acid followed by brief vortexing and light centrifugation in a microcentrifuge. The digest supernatants were subsequently transferred to secondary prewashed 500 μL microcentrifuge tubes and carefully concentrated using the Genevac to final volumes of 10-20 μL. At no stage were the digests taken to dryness, in order to avoid irreversible adsorption of low abundance peptides to the walls of the tubes.

The concentrated digests were then carefully decanted to avoid particulates and transferred to the wells of a V-bottom 220 μL polypropylene microtiter 96 well plate. This plate was directly placed in a Symbiot (Applied Biosystems, Foster City, CA) robotic MALDI target spotter and 0.5 μL aliquots were spotted on a 2 × 96 well PS1 MALDI target along with a 0.3 μL aliquot of alpha-hydroxycinnamic acid matrix in 50%ACN, 0.1%TFA. Between each row of sample spots, calibrant (Des Arg1 Bradykinin, M_r 904.4681; angiotensin 1, 1296.6853; Glu1-Fibrinopeptide B, 1570.6774; Neurotensin, 1672.9175) was spotted for close external calibration between each successive MALDI spectrum.

MALDI spectra were acquired on a Voyager DE-STR under the following conditions: positive reflectron mode with delayed extraction, accelerating voltage 20kV, grid voltage 65%, mirror voltage ratio 1.12, extraction delay time 125 nsec and low mass gate 500 Da. Spectral acquisition was automated using a spiral search pattern with saved spectra being the average of 3 successful acquisitions from 400 laser shots at 20 Hz repetition rate in the m/z 850-3000 range with a minimum intensity of 750 counts in the m/z 1000-3000 range. Peptide mass fingerprints were analyzed using the program Protein Prospector (Clauser, K. R. et al., 1999, *Analytical Chemistry* 71, 14:2871). Peaks from baseline corrected, noise filtered deisotoped spectra were filtered to remove autolytic trypsin and most keratin peaks and then subjected to two modes of analysis. The first involved tolerant matching of 4 or 5 peaks to proteins in the database within a 100ppm window. In general, proteins matching with MOWSE scores (see Pappin, D. J. C. et al., 1993, *Current Biology* 3: 327-332 for an

explanation of MOWSE scores) in excess of 10000 were considered hits. The second analysis involved using the program "intellical" (Applied Biosystems) which demands high precision. As a first pass, 25 proteins would be selected from the database with 3 matches with in 150 ppm mass accuracy. The program would then look for a uniform deviation between the observed and calculated peptide masses and recalibrate the spectrum against the best fits. In general, a protein was considered a hit that had 4 peptides matching within 15 ppm of the recalibrated spectrum and MOWSE scores over 1000 using these more rigorous parameters. These analyses were fully automated using PS1 software (Applied Biosystems). Figure 2 shows a representative example of a MALDI mass spectrum generated from polypeptides derived from a single one-dimensional gel slice.

As well as these selection criteria, the relative intensity of the matching peaks and the molecular weight of the identified protein relative to the band from which it was excised were also taken into account. The remaining portions of the digests were subjected to automated LC/MS/MS analysis. The microtiter plate containing the remaining peptide digest mixture were transferred to an Endurance autosampler connected to a MicroTech Ultimate LC system. The digest (10 μL) was transferred to a capillary trapping column containing C18 reversed phase resin at 20 μL /min using a third pump containing solvent A (95% water, 5% acetonitrile, 0.5% acetic acid) and washed for 3 min. A gradient of solvent A to solvent B (80% acetonitrile, 20% water, 0.5% acetic acid) 20% to 80% over 40 min was used to elute peptides through a 4.5 cm 75 μ C-18 packed Picofrit column (New Objectives Inc., Woburn, Massachusetts) at a flow rate of 200-500 nL/min directly into the heated capillary orifice of a Finnigan LCQ Ion Trap Mass spectrometer equipped with a Finnigan dynamic nanospray source (Thermo Finnigan, San Jose, California).

Mass spectra were acquired in the m/z 400-2000 range under the following conditions: positive polarity, capillary temperature 148°C, source voltage 2.4 kV, source current 80 μA, capillary voltage 29 V and tube lens offset 0 V. After one full scan MS of the column effluent was recorded, two MS/MS spectra of the

most intense and second most intense MS peaks were recorded over the m/z 100-2000 range with an isolation width of 2.5 and normalized collision energy 35. Dynamic exclusion was employed to select the maximum number of unique peptide peaks from the chromatograms. After replicate MS/MS spectra were acquired for a precursor ion, the m/z value of ion was placed on an exclusion list with a ± 1.5 u window for 3 min. Each chromatogram was subsequently analyzed with the program SEQUEST (Ducret et al., 1998, *Protein Sci.* 7: 706-719). The minimum requirement for a hit were at least 2 peptides for a particular protein having an $X_{corr} > 1.7$ for a +1 ion, $X_{corr} > 2$ for a +2 ion or $X_{corr} > 3$. In all cases Δ_{corr} must be greater than 0.1.

A set of 3025 polypeptides [SEQ ID NOS:1-3025] was identified in the GENBANK database on the basis of the above-described selection criteria for hits from the mitochondrial protein preparations recovered according to the procedures detailed above. Table 1 presents the numbers [SEQ ID NOS:1-3025] corresponding to the Sequence Listing submitted herewith for all 3025 polypeptides identified herein as mitochondrial components, along with the GENBANK accession numbers for these sequences and (if known) a brief description of each protein based on its sequence characteristics and database annotation. Additional polypeptides that were identified included those having amino acid sequences as set forth in NCBI/Genbank Acc. Nos. 35655 and 1421609, and reference herein to any one of SEQ ID NOS:1-3025 may according to certain embodiments be understood to include NCBI/Genbank Acc. Nos. 35655 and 142160.

TABLE 1

HUMAN HEART MITOCHONDRIAL PROTEINS

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1	13013	ND 4
2	28590	reading frame HSA
3	28714	anion transport protein
4	30102	type I collagen
5	31474	follicle stimulating hormone receptor
6	31645	glyceraldehyde 3-phosphate dehydrogenase
7	31746	glutathione-insulin transhydrogenase (216 AA)
8	34670	hexokinase 1
9	34719	myeloperoxidase
10	72146	vitronectin precursor - human
11	72222	heat shock protein 90-beta - human
12	86754	carrier ANT3 - human (fragment)
13	87528	dnaK-type molecular chaperone HSPA5 precursor - human
14	88512	protein-L-isoaspartate(D-aspartate) O-methyltransferase (EC 2.1.1.77) splice form II - human
15	88650	succinate dehydrogenase (ubiquinone) (EC 1.3.5.1) 27K iron-sulfur protein precursor, mitochondrial - human (fragment)
16	88741	T-cell receptor beta chain V region - human (fragment)
17	88972	undulin 1
18	105294	alternative splicing factor ASF-2
19	105475	myosin-binding protein C, skeletal muscle - human
20	105595	cell adhesion protein SQM1
21	106140	glycophorin A
22	106185	GTP-binding protein Rab2
23	106906	lipopolysaccharide-binding protein
24	106970	mcf2 protein
25	107554	pyruvate kinase isozyme M2
26	107631	ryanodine receptor type 1, skeletal muscle - human
27	107912	transcription factor E3
28	113962	annexin VI
29	114312	Sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (Calcium pump 2) (SERCA2) (SR Ca(2+)-ATPase 2) (Calcium-transporting ATPase sarcoplasmic reticulum type, slow twitch skeletal muscle isoform) (Endoplasmic reticulum class 1/2 Ca(2+) ATPase)
30	114374	Na,K-ATPase subunit alpha 1
31	114374	Sodium/potassium-transporting ATPase alpha-1 chain precursor (Sodium pump 1) (Na+/K+ ATPase 1)

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
32	114549	ATPase beta F1
33	115206	C-1-TETRAHYDROFOLATE SYNTHASE, CYTOPLASMIC (C1-THF SYNTHASE)
34	117103	cox 5b
35	117759	UCR 4 CYTOCHROME C1
36	117863	UCR cyt b
37	120643	GLYCERALDEHYDE 3-PHOSPHATE DEHYDROGENASE, MUSCLE
38	120749	MAJOR GASTROINTESTINAL TUMOR-ASSOCIATED PROTEIN GA733-2
39	121665	Glutathione peroxidase 1 (GSHPx-1) (Cellular glutathione peroxidase)
40	123277	HOMEOBOX PROTEIN HOX-C6(HHO.C8)
41	123571	heat shock 27KD protein
42	123678	heat shock 90kD protein HSP 90-ALPHA (HSP 86)
43	123678	Heat shock protein HSP 90-alpha (HSP 86)
44	125484	HEPATOCYTE GROWTH FACTOR RECEPTOR PRECURSOR(C-MET)(HGF-SF RECEPTOR)
45	129070	pyruvate dehydrogenase E1-beta
46	129379	heat shock 60 kDa protein, mitochondrial precursor (Hsp60) (60 kDa chaperonin) (CPN60) (Heat shock protein 60) (HSP-60) (Mitochondrial matrix protein P1) (P60 lymphocyte protein) (HuCHA60)
47	129902	Phosphoglycerate kinase 1 (Primer recognition protein 2) (PRP 2)
48	130749	ALKALINE PHOSPHATASE, TISSUE-NONSPECIFIC ISOZYME PRECURSOR
49	132164	RETINOBLASTOMA-ASSOCIATED PROTEIN(P105-RB)
50	136066	TRIOSEPHOSPHATE ISOMERASE
51	136090	TROPOMYOSIN BETA CHAIN, SKELETAL MUSCLE
52	136213	Troponin I, cardiac muscle
53.	141686	ZINC FINGER PROTEIN 8
54	177836	alpha-1-antitrypsin precursor
55	178345	alloalbumin Venezia
56	178390	aldehyde dehydrogenase
57	178426	alpha-fodrin
58	178736	apolipoprotein B100
59	178896	beta-3-adrenergic receptor
60	179279	ATPase beta subunit
61	180529	chromogranin A
62	181238	cytochrome c1
63	184477	retinoic acid receptor
64	188590	myosin light chain 3
65	188672	mannose 6-phosphate receptor

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
66	189422	proliferating cell nuclear protein P120
67	189514	p80-coilin
68	190201	porin
69	190474	salivary proline-rich protein 1
70	190804	ubiquinone-binding protein
71	190804	UCR 6 ubiquinone-binding protein
72	223374	isomerase,triosephosphate
73	223582	histone H4
74	223632	dismutase,Cu/Zn superoxide
75	224309	protein delta T3,glyco
76	225897	glycogen phosphorylase
77	225985	amyloid related serum protein SAA
78	226007	ventricular myosin L1
79	226021	growth regulated nuclear 68 protein
80	226209	cox 8
81	227297	ND FeS NADH dehydrogenase FeS protein
82	227448	phosphofructokinase
83	228097	receptor-like Tyr phosphatase
84	229149	hemoglobin beta
85	229479	lipoprotein Gln I
86	229479	lipoproteinGln I
87	230004	Human Neutrophil Elastase (HNE) (E.C.3.4.21.37) (Also Referred To As Human Leucocyte Elastase (HLE)) Complex With Methoxysuccinyl-Ala-Ala-Pro-Ala Chloromethyl Ketone (MSACK)
88	231743	G1/S-SPECIFIC CYCLIN D3
89	232472	nucleotide diphosphate kinase subunit A, p19/nm23-H1 [human, Peptide Partial, 12 aa, segment 1 of 3]
90	238427	Porin 31HM [human, skeletal muscle membranes, Peptide, 282 aa]
91	251188	protein phosphatase from PCR fragment H9
92	283950	oxoglutarate dehydrogenase (lipoamide) (EC 1.2.4.2) precursor - human
93	284319	mucin-associated antigen - human (fragment)
94	285975	rab GDI
95	292793	T-cell receptor beta
96	306926	insulin-like growth factor binding protein 2
97	307021	mu-immunoglobulin
98	312137	aldolase C
99	337758	pre-serum amyloid P component
100	338017	SEF2-1D protein
101	339647	thyroid hormone binding protein precursor
102	346275	myelin transcription factor 1 - human (fragment)
103	352335	reductase,NADH cytochrome b5

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
104	385479	N-methyl-D-aspartate glutamate receptor channel; NMDA GluR channel
105	386745	guanine nucleotide-binding protein G-s-alpha-3
106	386872	myoglobin
107	387010	pyruvate dehydrogenase E1-beta subunit precursor
108	387011	pyruvate dehydrogenase E1-alpha
109	387011	pyruvate dehydrogenase E1-alpha precursor
110	387016	phosphoglycerate mutase
111	393124	Unknown
112	416776	CD27 LIGAND(CD70 ANTIGEN)
113	434755	rat general mitochondrial matrix processing protease mRNA (RATMPP). , similar to
114	436222	Unknown
115	438650	paired box protein
116	448295	TLS protein
117	458862	heart fatty acid binding protein; hFABP
118	469045	h-contactin 2 precursor
119	476780	Ras guanine nucleotide exchange factor son-of-sevenless (sos) 1 - human
120	481043	MHC class III histocompatibility antigen HLA-B-associated protein 2 [similarity] - human
121	483239	homeotic protein engrailed 2 - human
122	499158	acetoacetyl-CoA thiolase mitochondrial
123	516764	motor protein
124	516768	motor protein
125	533538	diamine oxidase, copper/topa quinone containing
126	551604	pregnancy-specific beta-1 glycoprotein
127	553254	cytochrome b5 reductase (EC 1.6.2.2)
128	553597	myosin heavy chain beta-subunit
129	553734	putative
130	553734	Unknown
131	577307	The ha3662 gene product is related to mouse glycerophosphate dehydrogenase.
132	595267	gastrin-binding protein 78 kDa
133	606609	GBP
134	627364	adenovirus E1A-associated 130k protein - human
135	627367	desmoyokin - human (fragments)
136	631070	AHNAK-related protein - human (fragment)
137	687714	dynein heavy chain, isotype 1B
138	703083	cytochrome b5
139	704445	ATPase subunit 8
140	728834	Alu subfamily SB2 sequence contamination warning entry
141	802150	pancreatic peptidylglycine alpha-amidating monooxygenase; PA

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
142	903598	Krueppel-type zinc finger protein
143	992629	orf
144	1000865	This CDS feature is included to show the translation of the corresponding V_region. Presently translation qualifiers on V_region features are illegal
145	1001941	dihydropyridine receptor alpha 1 subunit
146	1033182	Y-chromosome RNA recognition motif protein
147	1053081	calpastatin
148	1065362	Adp-Ribosylation Factor 1 Complexed With Gdp, Full Length Non-Myristoylated
149	1070477	insulin receptor precursor - human
150	1071834	dihydrolipoamide S-succinyltransferase
151	1082355	epidermal autoantigen 450K (clone pE450-B) - human (fragment)
152	1082428	GTPase-activating protein rhoGAP
153	1082553	JC-kappa protein
154	1082567	laminin A3
155	1082692	phospholipase C beta 3
156	1082723	propionyl Coenzyme A carboxylase, beta polypeptide
157	1082723	propionyl-CoA carboxylase (EC 6.4.1.3) beta chain precursor - human
158	1085294	cell-cycle-dependent 350K nuclear protein - human (fragment)
159	1085373	protein disulfide-isomeraseER60 precursor
160	1091688	heat shock protein
161	1096024	isoAsp protein carboxyl methyltransferase
162	1096067	tat-associated protein
163	1103677	myosin-light-chain kinase
164	1124876	Krueppel-related DNA-binding protein
165	1130694	erythrocyte adducin alpha subunit
166	1136416	mitosis-specific chromosome segregation protein SMC1 of S.cerevisiae., similar to
167	1136741	predicted protein of 548 amino acids
168	1151113	PDE1C3
169	1160932	DRAL gene product gi|7209525|dbj|BAA92253.1| (AB038794) DRAL/Slim3/FHL2
170	1168719	C6.1A PROTEIN
171	1168781	EXTRACELLULAR CALCIUM-SENSING RECEPTOR PRECURSOR
172	1169072	APOPAIN PRECURSOR (CYSTEINE PROTEASE CPP32) (YAMA PROTEIN) (CPP-32) (CASPASE-3)
173	1169204	dodecenoyl-CoA Delta-isomerase
174	1170654	ANTIGEN KI-67
175	1172554	VDAC-2
176	1174572	Thromboxane A2 receptor (TXA2-R) (Prostanoid TP receptor)

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
177	1177230	zinc finger
178	1177438	brca2
179	1184699	tyrosyl-tRNA synthetase
180	1196398	Unknown
181	1196433	Unknown
182	1220311	elongation factor-1 alpha
183	1235848	HMG CoA synthase
184	1235902	FRAP-related protein
185	1237406	Cu/Zn-superoxide dismutase
186	1245894	cardiac myosin binding protein-C
187	1245985	beta 2-adrenergic receptor, beta 2AR {Y354A} [human, Peptide Partial Mutagenesis, 24 aa]
188	1246236	ptp-IV1b, PTP-IV1 gene product
189	1262579	ND 1
190	1262580	ND 2
191	1262581	cox 1
192	1262582	ATPase 6
193	1292941	hydroxymethylglutaryl-CoA lyase
194	1293561	Diff40 gene product
195	1335064	fibrillin
196	1335072	G34 (big gastrin)
197	1335212	medullasin N-term.
198	1335250	Rod cGMP phosphodiesterase
199	1335277	Unknown
200	1340142	alpha1-antichymotrypsin
201	1346317	heat shock 70kD protein 7
202	1351900	NEUROBLAST DIFFERENTIATION ASSOCIATED PROTEIN
203	1351900	[Segment 1 of 2] Neuroblast differentiation associated protein AHNAK (Desmoyokin)
204	1351901	NEUROBLAST DIFFERENTIATION ASSOCIATED PROTEIN
205	1354222	aldehyde dehydrogenase E3
206	1359715	Na+,K+ ATPase
207	1359715	Na+,K+ ATPase
208	1359759	histamine H2 receptor
209	1362755	endopeptidase La homolog (EC 3.4.21.-) precursor, mitochondrial (version 1)
210	1381814	skeletal muscle LIM-protein SLIM
211	1399105	phosphatidylinositol (4,5)bisphosphate 5-phosphatase homolog
212	1399801	p167
213	1408188	desmin
214	1504020	Yeast translation activator GCN1 (P1:A48126) , similar to
215	1517899	RAGE-1 ORF5; one of 3 possible coding regions
216	1582692	TATA box-binding protein

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
217	1587138	sorcin
218	1587477	TCOF1 gene
219	1588292	Ca channel:SUBUNIT=alpha:ISOTYPE=L
220	1655594	HES1
221	1657266	S10 GTP-binding protein
222	1665723	RPD3 protein
223	1688267	polo like kinase
224	1706611	ELONGATION FACTOR TU, MITOCHONDRIAL PRECURSOR
225	1708098	Histone H1t
226	1709123	DNA MISMATCH REPAIR PROTEIN MSH6 (MUTS-ALPHA 160 KDA SUBUNIT
227	1709947	PYRUVATE CARBOXYLASE PRECURSOR
228	1710279	dihyrolipoamide acetyl transferase
229	1718502	aconitase mitochondrial
230	1718502	aconitase, mitochondrial
231	1730078	130 KDA LEUCINE-RICH PROTEIN(GP130)
232	1731414	ZINC FINGER PROTEIN 138
233	1762533	carnitine palmitoyltransferase I
234	1763238	lysosomal trafficking regulator LYST
235	1773381	APXL
236	1778410	unknown
237	1778432	Treacher Collins syndrome
238	1805280	alpha II spectrin
239	1869803	fatty acid binding protein 3
240	1930110	GM-CSF receptor alpha subunit soluble 3
241	1942187	Lactoferrin, H253m N Terminal Lobe Of Human
242	1943532	Profilin I Crystallized In High Salt Actin-Binding Protein, Human Platelet
243	2078329	3-hydroxyacyl-CoA dehydrogenase, isoform 2
244	2078470	Putative gene. Genscan predictions confirmed by EST splicing.; coded for by human cDNAs AA122029 (NID:g1678048), D31562 (NID:g644442), AA158721 (NID:g1733515), R59640 (NID:g830335) and F13082 (NID:g709111)
245	2114493	RNA editase
246	2117022	zinc finger 5 protein
247	2117163	leukocyte antigen, HLA-A2 variant
248	2117707	dihydrolipoamide S-(2-methylpropanoyl)transferase (EC 2.3.1.-) precursor - human
249	2117873	pyruvate kinase (EC 2.7.1.40), muscle splice form M1 - human
250	2118344	arginine--tRNA ligase (EC 6.1.1.19) - human
251	2118970	histone H1 - human (fragment)
252	2119268	alpha-tubulin - human (fragment)
253	2119390	proapo-A-I protein - human

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
254	2119533	giantin
255	2119712	dnaK-type molecular chaperone HSPA1L heat shock protein
256	2119918	P43 - human
257	2134903	CG1 protein, kinectin 1
258	2135068	enhancer protein
259	2135611	melanoma ubiquitous mutated protein - human (fragment)
260	2135819	neuropolypeptide h3, brain
261	2135911	3',5'-cyclic-nucleotide phosphodiesterase (EC 3.1.4.17) 4A, cAMP-specific, long splice form - human
262	2136207	succinate-semialdehyde dehydrogenase (EC 1.2.1.24) - human (fragment)
263	2136282	TOG protein
264	2144337	pyruvate dehydrogenase (lipoamide) (EC 1.2.4.1) beta chain precursor, long splice form - human
265	2145011	putative collagen homolog protein-b
266	2146960	methyl CpG binding protein 2 - human (fragment)
267	2217933	PKU-beta
268	2224581	Unknown
269	2224583	Unknown
270	2224621	Unknown
271	2224663	Unknown
272	2243110	Unknown
273	2244654	HS24/P52
274	2270925	beta4-integrin
275	2286145	caspase-like apoptosis regulatory protein
276	2293556	Ran binding protein 2
277	2306809	X-linked nuclear protein
278	2317769	probable zinc finger protein H101
279	2393734	C. elegans F11A10.5; 80% similarity to Z68297 (PI
280	2393763	NAD (H)-specific isocitrate dehydrogenase gamma subunit
281	2454586	reverse transcriptase
282	2465178	COX7RP
283	2498864	RRP5 PROTEIN HOMOLOG
284	2499753	PROTEIN-TYROSINE PHOSPHATASE KAPPA PRECURSOR
285	2506118	MULTIDRUG RESISTANCE PROTEIN 1
286	2507187	PROTEIN-L-ISOASPARTATE(D-ASPARTATE) O-METHYLTRANSFERASE (PROTEIN-BETA-ASPARTATE METHYLTRANSFERASE) (PIMT)
287	2511440	calcium/calmodulin-dependent protein kinase II; CaM kinase II
288	2511779	beta III spectrin
289	2565032	transcription activator/repressor protein delta/YY1; similar
290	2624694	Single-Stranded Dna Binding Protein,Human Mitochondrial
291	2653817	lipopolysaccharide binding protein

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
292	2661211	oxidative 3 alpha hydroxysteroid dehydrogenase
293	2662397	HADHB
294	2665782	voltage-gated sodium channel, subtype III
295	2695574	leukocyte function-associated molecule-1 alpha subunit
296	2769254	NIPSNAP2 protein
297	2769254	NIPSNAP2 protein
298	2811135	retinal rod Na+/Ca+, K+ exchanger
299	2822143	R30217_1
300	2852604	Unknown
301	2865252	Unknown
302	2873377	exportin t
303	2981731	Cypa Complexed With Hagpia
304	3012097	F22329_1
305	3021386	zinc finger protein
306	3023143	kappa 1 immunoglobulin light chain variable region
307	3043584	Unknown
308	3043646	Unknown
309	3046880	LIM-homeodomain protein LMX1B/LMX1.2
310	3114510	T State Human Hemoglobin [alpha V96w], Alpha Aquomet, Beta Deoxy
311	3123721	ND 24K NADH dehydrogenase 24-kDa subunit of complex I
312	3153859	thioredoxin delta 3
313	3168604	proline and glutamic acid rich nuclear protein isoform
314	3211975	putative glialblastoma cell differentiation-related protein
315	3211977	sarco-/endoplasmic reticulum Ca-ATPase 3
316	3212539	Isovaleryl-Coa Dehydrogenase At 2.6 Angstroms Resolution: Structural Basis For Substrate Specificity
317	3252827	Unknown
318	3252827	Unknown
319	3256185	target of myb1homolog)
320	3273228	acyl-CoA dehydrogenase very-long-chain
321	3273386	plasmalemmal porin
322	3294170	dJ232K4.1 (hypothetical 141.7 kD protein JUMONJI)
323	3299887	ES/130-related protein
324	3327040	Unknown
325	3327054	Unknown
326	3327054	Unknown
327	3360457	cul-3
328	3402141	Lysozymes At Constant Positions
329	3402145	Lysozyme
330	3540239	ND Fe-S2 NADH dehydrogenase-ubiquinone Fe-S protein 2 precursor
331	3599521	musculin

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
332	3641621	gp180-carboxypeptidase D-like enzyme
333	3641621	gp180-carboxypeptidase D-like enzyme
334	3660040	Fkbp Mutant F36v Complexed With Remodeled Synthetic Ligand
335	3660556	hdkk-4
336	3694663	Unknown
337	3717965	DIA-12C
338	3766197	succinyl-CoA synthetase beta subunit ,ATP-specific
339	3766197	succinyl-CoA synthetase beta subunit ,ATP-specific
340	3766199	succinyl-CoA synthetase beta subunit GTP-specific
341	3766451	CHRNB2
342	3882147	Unknown
343	3882301	Unknown
344	3885362	sepiapterin reductase
345	3891975	Cathepsin G
346	3982589	SOX-28 protein
347	3986482	translation initiation factor eIF3 p40 subunit; eIF3p40
348	4008131	chaperonin 10
349	4096860	fibronectin
350	4097409	PAX-9
351	4103446	NAD+-specific isocitrate dehydrogenase beta subunit isoform A
352	4127947	guanine nucleotide-exchange factor
353	4139720	Chymase
354	4151929	PCAF-associated factor 400
355	4153874	single-stranded mitochondrial DNA-binding protein precursor
356	4204963	MUC-1/X mucin short variant
357	4206175	ubiquitin-specific protease
358	4210351	novel protein
359	4240227	Unknown
360	4240243	Unknown
361	4240305	Unknown
362	4261577	CD8 beta chain
363	4262430	CMP-NeuAc:lactosylceramide alpha-2,3-sialyltransferase
364	4263556	Unknown
365	4406346	guanylate cyclase activating protein 3
366	4406564	succinyl-CoA synthetase beta subunit GTP-specific
367	4406651	h-sco1
368	4416457	mitotic checkpoint protein
369	4495063	yeast suppressor protein SRP40) dJ108K11.3 (similar to
370	4501869	acyl-Coenzyme A oxidase 2, branched chain
371	4501967	alpha-2C-adrenergic receptor; alpha-2C-1 adrenergic receptor; alpha-2C-1 adrenoceptor; alpha-2-adrenergic receptor, renal type; alpha2-AR-C4
372	4502011	adenylate kinase 1

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
373	4502013	adenylate kinase 2 isoform a; Adenylate kinase-2, mitochondrial
374	4502097	solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 4; adenine nucleotide translocator 1 (skeletal muscle)
375	4502101	annexin I
376	4502107	annexin V
377	4502111	annexin VII isoform 1
378	4502201	ADP-ribosylation factor 1
379	4502273	ATPase, Na+/K+ transporting, alpha 3 polypeptide
380	4502297	ATPase delta F1
381	4502303	ATPase OSCP F1
382	4502327	AU RNA-binding protein/enoyl-Coenzyme A hydratase precursor
383	4502331	arginine vasopressin receptor 1A; V1a vasopressin receptor; vascular/hepatic-type arginine vasopressin receptor; antidiuretic hormone receptor 1A
384	4502379	BCL10
385	4502419	biliverdin reductase B (flavin reductase (NADPH))
386	4502457	ATP-binding cassette, sub-family B (MDR/TAP), member 11; ABC member 16, MDR/TAP subfamily
387	4502459	basigin; collagenase stimulatory factor; M6 antigen
388	4502509	complement component 5 receptor 1 (C5a ligand); complement component-5 receptor-2 (C5a ligand)
389	4502517	carbonic anhydrase I
390	4502563	calpain 2, large subunit
391	4502601	carbonyl reductase 3; carbonyl reductase3 [Homo sap
392	4502603	chromobox homolog 4 (Pc class homolog, Drosophila); chromobox homolog 4 (Drosophila Pc class)
393	4502703	CDC6 homolog; CDC6 (cell division cycle 6, S. cerevisiae) homolog; CDC18 (cell division cycle 18, S.pombe, homolog)-like; CDC6-related protein
394	4502719	cadherin 13 preproprotein; H-cadherin; heart-cadherin; T-cad
395	4502841	carbohydratesulfotransferase 1
396	4502855	sarcomeric mitochondrial creatine kinase precursor; creatine kinase, mitochondrial 2; basic-type mitochondrial creatine kinase
397	4502985	cox 6b
398	4502987	cox 7a muscle
399	4502989	cox 7a liver
400	4502991	cox 7b
401	4502993	cox 7c
402	4503015	copine III
403	4503021	liver carnitine palmitoyltransferase I; L-CPT1
404	4503049	cysteine-rich protein 2; Cystein-rich intestinal protein
405	4503057	crystallin, alpha B; crystallin, alpha-2; Rosenthal fiber component; heat-shock 20 kD like-protein

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
406	4503143	cathepsin D
407	4503177	chromosome X open reading frame 2
408	4503269	deoxycytidine kinase gi|11436224|ref|XP_00347
409	4503301	2,4-dienoyl CoA reductase 1 precursor
410	4503375	dihydropyrimidinase
411	4503431	dysferlin; dystrophy-associated fer-1-like 1
412	4503443	endothelin converting enzyme 1
413	4503447	peroxisomal enoyl-coenzyme A hydratase-like protein; delta3,5-delta2,4-dienoyl-CoA isomerase; peroxisomal enoyl-CoA hydratase 1; dienoyl-CoA isomerase
414	4503475	eukaryotic translation elongation factor 1 alpha 2
415	4503507	eukaryotic translation initiation factor 2, subunit 3
416	4503537	eukaryotic translation initiation factor 4E binding protein 3
417	4503607	electron transfer flavoprotein alpha polypeptide
418	4503609	electron transfer flavoprotein beta polypeptide
419	4503613	envoplakin
420	4503651	fatty-acid-Coenzyme A ligase, long-chain 1
421	4503667	fibrillin 2+F422
422	4503731	FK506-binding protein 6
423	4503835	frizzled 9
424	4503843	adaptor-related protein complex 1, gamma 2 subunit; gamma2-a
425	4503899	N-acetylgalactosamine-6-sulfatase precursor
426	4503937	glioblastoma amplified sequence
427	4504041	guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 2; Guanine nucleotide-binding protein (G protein), alpha-inhibiting
428	4504049	guanine nucleotide binding proteintransducin alpha-chain
429	4504067	aspartate aminotransferase 1; glutamic-oxaloacetic transamin
430	4504071	platelet glycoprotein Ib alpha polypeptide precursor
431	4504169	glutathione synthetase
432	4504189	glutathione transferase zeta 1 (maleylacetoacetate isomerase); glutathione transferase Zeta 1
433	4504483	hypoxanthine phosphoribosyltransferase 1
434	4504487	histidine-rich calcium-binding protein precursor SARCOPLASMIC RETICULUM
435	4504517	heat shock 27kD protein 1
436	4504521	heat shock 60kD protein 1 (chaperonin)
437	4504523	heat shock 10kD protein 1 (chaperonin 10)
438	4504523	heat shock 10kD protein 1 (chaperonin 10)
439	4504665	interleukin 2 receptor, beta; Interleukin-2 receptor, beta polypeptide
440	4504689	IMP (inosine monophosphate) dehydrogenase 2
441	4504733	insulin receptor substrate 4
442	4504795	inositol 1,4,5-triphosphate receptor, type 3

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
443	4504867	ring finger protein (C3HC4 type) 8; C3HC4-type zinc finger protein; zinc finger protein
444	4504975	low density lipoprotein receptor precursor; LDLR precursor; LDL receptor
445	4504991	leukemia inhibitory factor (cholinergic differentiation factor); cholinergic differentiation factor
446	4505071	MAP-kinase activating death domain protein
447	4505093	monoamine oxidase B
448	4505093	monoamine oxidase B
449	4505145	malic enzyme 2, NAD(+)-dependent, mitochondrial
450	4505145	malic enzyme 2, NAD(+)-dependent, mitochondrial; Malic enzyme, mitochondrial; malic enzyme 2, mitochondrial; pyruvic-malic carboxylase; malate dehydrogenase
451	4505153	MAP/ERK kinase kinase 3
452	4505249	mutS homolog 3 (E. coli); mutS (E. coli) homolog 3
453	4505257	moesin
454	4505257	moesin
455	4505355	ND B8
456	4505357	ND 9k NDUFA4
457	4505359	ND B14
458	4505361	ND B12
459	4505363	ND 16k, SGDH
460	4505365	ND B17
461	4505367	ND 6k
462	4505369	ND 18K NADH dehydrogenase (ubiquinone) Fe-S protein 4 (18kD) (NADH-coenzyme Q reductase); NADH dehydrogenase (ubiquinone) Fe-S protein 4, 18kD (NADH-coenzyme Q; mitochondrial respiratory chain complex I (18-KD subunit)
463	4505371	ND 23K NADH dehydrogenase (ubiquinone) Fe-S protein 8 (23kD) (NADH-coenzyme Q reductase); NADH dehydrogenase (ubiquinone) Fe-S protein 8 (23kD) (NADH-coenzyme Q
464	4505375	neogenin homolog 1 (chicken); neogenin (chicken) homolog 1
465	4505399	NIPSNAP homolog 1; 4-nitrophenylphosphatase domain and non-neuronal SNAP25-like 1
466	4505405	glycoprotein (transmembrane) nmb; transmembrane glycoprotein
467	4505591	peroxiredoxin 1; Proliferation-associated gene A; proliferation-associated gene A (natural killer-enhancing factor A)
468	4505621	prostatic binding protein; phosphatidylethanolamine binding protein
469	4505685	pyruvate dehydrogenase (lipoamide) alpha 1; Pyruvate dehydrogenase, E1-alpha polypeptide-1
470	4505687	pyruvate dehydrogenase (lipoamide) beta; Pyruvate dehydrogenase, E1 beta polypeptide
471	4505693	pyruvate dehydrogenase kinase, isoenzyme 4
472	4505717	peroxisomal biogenesis factor 11A

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
473	4505773	Prohibitin
474	4505775	carrier phosphate isoform B
475	4505775	phosphate carrier precursor isoform 1b; phosphate carrier, mitochondrial; phosphate carrier, mitochondrial precursor
476	4505801	phosphoinositide-3-kinase, class 3
477	4505869	phospholipase C, gamma 1 (formerly subtype 148)
478	4505887	phospholamban
479	4505893	proteolipid protein 2
480	4505909	peripheral myelin protein 2; M-FABP
481	4505911	postmeiotic segregation 1; Postmeiotic segregation increased (S. cerevisiae)-like 1
482	4505925	putative neurotransmitter receptor
483	4505965	POU domain, class 4, transcription factor 3
484	4506077	protein kinase C substrate 80KD-H
485	4506091	mitogen-activated protein kinase 6
486	4506189	proteasome (prosome, macropain) subunit, alpha type, 7
487	4506197	proteasome (prosome, macropain) subunit, beta type, 3; Proteasome subunit, beta type, 3
488	4506291	protein tyrosine phosphatase, non-receptor type 2, isoform 1; T-cell protein tyrosine phosphatase
489	4506371	RAB5B, member RAS oncogene family
490	4506401	raf proto-oncogene serine/threonine protein kinase
491	4506413	RAP1A, member of RAS oncogene family; RAS-related protein RAP1A
492	4506445	RNA binding motif protein 4
493	4506517	regulator of G-protein signalling 2, 24kD
494	4506787	IQ motif containing GTPase activating protein 1; rasGAP-like with IQ motifs
495	4506959	TAL1 (SCL) interrupting locus; SCL interrupting locus
496	4506975	carrier family 12 (sodium/potassium/chloride transporters), member 2
497	4506977	carrier family 12 (sodium/chloride transporters), member 3
498	4506997	solute carrier family 25 (mitochondrial carrier; oxoglutarate carrier), member 11; solute carrier family 20 (oxoglutarate carrier), member 4
499	4507007	carrier family 25 (mitochondrial carrier, Aralar), member 12; calcium binding mitochondrial carrier superfamily member Aralar
500	4507021	solute carrier family 4, anion exchanger, member 1 (erythrocyte membrane protein band 3, Diego blood group)
501	4507185	sepiapterin reductase (7,8-dihydrobiopterin:NADP+ oxidoreductase); Sepiapterin reductase
502	4507215	signal recognition particle 54kD

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
503	4507299	sudD suppressor of bimD6 homolog (A. nidulans); human homolog of Aspergillus nidulans sudD gene product; sudD (suppressor of bimD6, Aspergillus nidulans) homolog
504	4507389	elongin A; transcription elongation factor B (SIII)
505	4507401	transcription factor 6-like 1
506	4507401	transcription factor 6-like 1 (mitochondrial transcription factor 1-like)
507	4507431	thyrotrophic embryonic factor; Thyrotroph embryonic factor
508	4507443	transcription factor AP-2 beta (activating enhancer binding protein 2 beta); transcription factor AP-2 beta (activating enhancer-binding protein 2 beta)
509	4507609	tumor necrosis factor (ligand) superfamily, member 9
510	4507643	tumor protein D52-like 2; hD54
511	4507645	triosephosphate isomerase 1
512	4507645	triosephosphate isomerase 1
513	4507665	tyrosylprotein sulfotransferase 1
514	4507677	tumor rejection antigen (gp96) 1; Tumor rejection antigen-1 (gp96)
515	4507713	tetratricopeptide repeat domain 2
516	4507733	Tu translation elongation factor, mitochondrial
517	4507783	ubiquitin-conjugating enzyme E2H (homologous to yeast UBC8)
518	4507789	ubiquitin-conjugating enzyme E2L 3
519	4507793	ubiquitin-conjugating enzyme E2N
520	4507841	ubiquinol-cytochrome c reductase core protein I
521	4507843	ubiquinol-cytochrome c reductase core protein II
522	4507853	ubiquitin specific protease, proto-oncogene; Unph
523	4507857	ubiquitin specific protease 7 (herpes virus-associated)
524	4507879	voltage-dependent anion channel 1
525	4507913	WAS protein family, member 1; WASP family Verprolin-homologous protein; scar, dictyostelium, homology of, 1
526	4507953	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide; Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation
527	4507963	zinc finger protein homologous to Zfp37 in mouse
528	4507979	zinc finger protein 132
529	4522026	Bassoon protein; match to PID:g3043642; similar to PID:g3413810 , C-terminus matches KIAA0559, N-terminus similar to
530	4529887	NG35
531	4557032	lactate dehydrogenase B
532	4557036	microseminoprotein, beta
533	4557044	propionyl Coenzyme A carboxylase, beta polypeptide
534	4557235	acyl-CoA dehydrogenase very long chain
535	4557247	acylphosphatase 2, muscle type
536	4557265	beta-1-adrenergic receptor gi|15298066|ref|XP
537	4557305	aldolase A protein

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
538	4557311	adenosine monophosphate deaminase 1 (isoform M)
539	4557317	annexin XI
540	4557365	Bloom syndrome protein
541	4557403	carnitine/acylcarnitine translocase; Carnitine-acylcarnitine translocase; carnitine-acylcarnitine carrier; solute carrier family 25 (carnitine/acylcarnitine translocase), member 20
542	4557403	carrier carnitine-acylcarnitine translocase
543	4557409	cardiac calsequestrin 2
544	4557439	cyclin-dependent kinase 3
545	4557451	chromodomain helicase DNA binding protein 3; Mi-2a; zinc-finger helicase (Snf2-like)
546	4557565	excision repair cross-complementing rodent repair deficiency, complementation group 6
547	4557579	fatty acid binding protein 4, adipocyte; A-FABP
548	4557657	immature colon carcinoma transcript 1
549	4557735	monoamine oxidase A
550	4557759	myeloperoxidase
551	4557765	5-methyltetrahydrofolate-homocysteine methyltransferase; 5-methyltetrahydrofolate-homocysteine methyltransferase 1
552	4557767	methylmalonyl Coenzyme A mutase precursor
553	4557769	mevalonate kinase
554	4557771	protein C, cardiac; myosin-binding protein C, cardiac
555	4557775	myosin light chain 2
556	4557817	Succinyl CoA:3-oxoacid CoA transferase
557	4557817	Succinyl CoA:3-oxoacid CoA transferase; succinyl-CoA:3-ketoacid-CoA transferase precursor
558	4557833	Propionyl-Coenzyme A carboxylase, alpha polypeptide
559	4557845	ribonucleotide reductase M2 polypeptide
560	4557867	sulfite oxidase
561	4557867	sulfite oxidase ,mitochondrial
562	4557876	ATP-binding cassette, sub-family A member 4; ATP binding cassette transporter; ATP-binding transporter, retina-specific; rim protein
563	4587083	MRP5
564	4589504	Unknown
565	4589644	Unknown
566	4678807	Unknown
567	4680705	CGI-33 protein
568	4680721	thyroid peroxidase
569	4689104	ND ASHI
570	4730927	spermatogenesis associated PD1
571	4757732	programmed cell death 8 (apoptosis-inducing factor)
572	4757762	ring finger protein 14; androgen receptor associated protein

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
573	4757786	N-acylsphingosine amidohydrolase (acid ceramidase)
574	4757852	BCS1 (yeast homolog)-like
575	4758024	coilin; coilin p80
576	4758030	coatomer protein complex, subunit alpha; alpha coat protein; xenin
577	4758038	cox 5a
578	4758040	cox 6c
579	4758118	mitochondrial ribosomal protein S29, 28S death associated protein 3;
580	4758118	mitochondrial ribosomal protein S29, 28S death associated protein 3;
581	4758120	death-associated protein 1
582	4758156	diacylglycerol kinase, iota
583	4758192	serine/threonine kinase 17a (apoptosis-inducing)
584	4758242	early development regulator 2; homolog of polyhomeotic 2
585	4758312	electron-transferring-flavoprotein dehydrogenase
586	4758352	ferredoxin 1 precursor; adrenodoxin
587	4758490	GTP binding protein 1
588	4758498	hexose-6-phosphate dehydrogenase precursor
589	4758504	hydroxyacyl-Coenzyme A dehydrogenase, type II
590	4758520	hect domain and RLD 2
591	4758520	hect domain and RLD 2
592	4758570	heat shock 70kD protein 9B (mortalin-2); heat shock 70kD protein 9 (mortalin); Heat-shock 70kD protein-9 (mortalin); mot-2; mthsp75
593	4758582	isocitrate dehydrogenase 3 (NAD+) gamma
594	4758604	interleukin enhancer binding factor 3, 90kD; M-phase phosphoprotein 4; nuclear factor associated with dsRNA
595	4758664	acetylglucosaminyltransferase-like protein
596	4758682	protease, serine, 15; Lon protease-like protein
597	4758714	microsomal glutathione S-transferase 3
598	4758750	myosin IXB
599	4758768	ND 42k
600	4758772	ND B9
601	4758774	ND 22k, PDSW
602	4758776	ND 7k
603	4758778	ND 8k, AGGG
604	4758784	ND B14.5
605	4758786	ND 49k
606	4758788	ND 30k
607	4758790	ND 15k
608	4758792	ND 13k-A
609	4758818	Notch homolog 4 (Drosophila); Notch, drosophila, homolog of, 4; Notch (Drosophila) homolog 4

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
610	4758832	neuregulin 2 isoform 1; neural- and thymus-derived activator for ErbB kinases
611	4758852	organic cation transporter like 3
612	4758940	chromosome 14 open reading frame 2; mitochondrial proteolipid 68MP homolog
613	4758940	mitochondrial proteolipid 68MP homolog
614	4759020	RAB5C, member RAS oncogene family; RAB, member of RAS oncogene family-like; RAB5C, member of RAS oncogene family
615	4759068	cytochrome oxidase deficient homolog 1
616	4759080	succinate dehydrogenase complex, subunit A, flavoprotein precursor; succinate dehydrogenase complex flavoprotein subunit precursor
617	4759080	succinate dehydrogenase, subunit A, flavoprotein (Fp)
618	4759082	serum deprivation response (phosphatidylserine-binding protein)
619	4759112	solute carrier family 16 (monocarboxylic acid transporters), member 3; monocarboxylate transporter 3
620	4759144	carrier family 9 (sodium/hydrogen exchanger), isoform 5
621	4759146	slit homolog 2 (Drosophila); slit (Drosophila) homolog 2
622	4759160	small nuclear ribonucleoprotein D3 polypeptide
623	4759196	symplekin
624	4760549	IDN3
625	4761539	voltage-dependent calcium channel alpha 1G subunit b isoform
626	4826643	annexin A3
627	4826649	mitochondrial ribosomal protein L49
628	4826649	mitochondrial ribosomal protein L49; chromosome 11 open reading frame 4
629	4826655	calbindin 1
630	4826661	nuclear receptor subfamily 1, group I, member 3
631	4826661	nuclear receptor subfamily 1, group I, member 3; constitutive androstane receptor-beta; orphan nuclear hormone receptor
632	4826772	insulin-like growth factor binding protein, acid labile subunit
633	4826848	ND B13
634	4826850	ND B14.5a NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 7 (14.5kD, B14.5a)
635	4826852	ND 8k
636	4826856	ND 75K NADH dehydrogenase (ubiquinone) Fe-S protein 1 (75kD) (NADH-coenzyme Q reductase); NADH dehydrogenase (ubiquinone), Fe-S protein-1 (75kD); NADH-ubiquinone oxidoreductase 75 kD subunit precursor
637	4826898	profilin 1
638	4826914	phospholipase A2, group IVB
639	4826950	kallikrein 7
640	4827065	zinc finger protein 147
641	4877291	receptor for Advanced Glycation End Products

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
642	4885281	glutamate dehydrogenase 1
643	4885331	G protein-coupled receptor 42
644	4885389	hydroxyacyl glutathione hydrolase; glyoxalase 2
645	4885389	hydroxyacyl glutathione hydrolase; hydroxyacyl glutathione hydrolase; glyoxalase 2; Hydroxyacyl glutathione hydrolase; glyoxalase II; hydroxyacylglutathione hydroxylase
646	4885401	cytochrome c heme lyase
647	4885533	peptidylglycine alpha-amidating monooxygenase COOH-terminal
648	4885553	postmeiotic segregation increased 2-like 9
649	4885565	peroxisomal acyl-CoA thioesterase
650	4885615	signal transducer and activator of transcription 2, 113kD
651	4885665	achaete-scute complex homolog-like 2; achaete-scute complex (Drosophila) homolog-like 2
652	4887552	MUC-B1
653	4894370	ND B22
654	4914601	Unknown
655	4929697	CGI-114 protein
656	5031609	branched chain alpha-ketoacid dehydrogenase kinase
657	5031631	CD36 antigen
658	5031691	chromosome 21 open reading frame 33; human HES1 protein, homolog to E.coli and zebrafish ES1 protein
659	5031707	glycoprotein A repetitions predominant precursor; garpin
660	5031777	isocitrate dehydrogenase 3 (NAD+) alpha
661	5031777	isocitrate dehydrogenase 3 alpha
662	5031875	lamin A/C
663	5031881	leucyl/cystinyl aminopeptidase; leucyl/cystinyl aminopeptidase (oxytocinase)
664	5031943	transcription factor NSCL-1 helix-loop-helix protein
665	5031987	peptidylprolyl isomerase F MITOCHONDRIAL PRECURSOR(
666	5032017	RAD50 (S. cerevisiae) homolog
667	5032051	ribosomal protein S14 40S
668	5032095	carrier family 21 (prostaglandin transporter), member 2
669	5032181	translocase of inner mitochondrial membrane Tim17b
670	5032215	translational inhibitor protein
671	5051381	FK506 binding protein 12-rapamycin associated protein 1
672	5059062	pilin-like transcription factor
673	5114261	voltage-dependent anion channel isoform 2
674	5138999	NADH-Ubiquinone reductase
675	5174539	malate dehydrogenase 1, NAD (soluble)
676	5174539	malate dehydrogenase 1, NAD (soluble); Malate dehydrogenase, soluble
677	5174541	malate dehydrogenase 2, NAD (mitochondrial); Malate dehydrogenase, mitochondrial

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
678	5174563	MHC binding factor, beta
679	5174627	plasma glutamate carboxypeptidase; aminopeptidase
680	5174739	tubulin, beta, 5
681	5174743	ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1
682	5360087	NY-REN-6 antigen
683	5453549	thioredoxin peroxidase; thioredoxin peroxidase (antioxidant enzyme)
684	5453559	ATPase d F0
685	5453670	golgi transport complex 1 (90 kD subunit); golgi transport complex 1 (90 kDa subunit)
686	5453750	brain acid-soluble protein 1; neuronal tissue-enriched acidic protein
687	5453890	PIBF1 gene product
688	5453902	NIMA-interacting, 4 (parvulin) peptidyl-prolyl cis-trans isomerase EPVH
689	5453990	proteasome (prosome, macropain) activator subunit 1 (PA28 alpha)
690	5454028	related RAS viral (r-ras) oncogene homolog; Oncogene RRAS
691	5454122	translocase of inner mitochondrial membrane Tim23
692	5454148	UNC13
693	5454152	ubiquinol-cytochrome c reductase binding protein
694	5454180	zinc finger protein 193
695	5578989	Unknown
696	5689405	Unknown
697	5689555	Unknown
698	5701717	UDP-N-acetylglucosamine:alpha-1,3-D-mannoside beta-1,4-N-acetylglucosaminyltransferase IV-homologue
699	5725250	G7 protein
700	5725370	involved in chromosomal translocation
701	5729802	Unknown
702	5729875	progesterone binding protein
703	5729877	heat shock 70kD protein 8; heat shock 70kD protein 8 (HSP73); heat shock cognate protein, 71-kDa; heat shock 70kd protein 10 (HSC71)
704	5729887	IQ motif containing GTPase activating protein 2 , RasGAP-related protein
705	5729937	metaxin 2
706	5729937	metaxin 2
707	5729966	MHC class I region ORF
708	5730027	GAP-associated tyrosine phosphoprotein p62 (Sam68)
709	5730033	sodium channel, voltage-gated, type X, alpha polypeptide
710	5730110	ubiquitin specific protease 3 gi|10720340|sp|Q9Y6I4|UBP3_HUMAN UBIQUITIN CARBOXYL-TERMINAL HYDROLASE 3
711	5759173	succinate dehydrogenase flavoprotein subunit

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
712	5802182	PPAR gamma coactivator-1
713	5802814	Gag-Pro-Pol-Env protein
714	5802970	AFG3 (ATPase family gene 3, yeast)-like 2
715	5803115	mitofilin inner membrane protein, mitochondrial (mitofilin); motor protein
716	5803135	RAB35, member RAS oncogene family; ras-related protein rab-1
717	5803149	coated vesicle membrane protein
718	5803159	sex comb on midleg (Drosophila)-like 1
719	5803201	transmembrane trafficking protein
720	5803207	U2 small nuclear RNA auxillary factor 1; U2 snRNP auxiliary factor small subunit; splicing factor U2AF 35kDa subunit
721	5821952	Rotamer Strain As A Determinant Of Protein Structural Specificity
722	5882259	genethonin 3
723	5901896	ATPase epsilon F1
724	5901926	cleavage and polyadenylation specific factor 5, 25 kD subunit
725	5901982	isocitrate dehydrogenase 3 (NAD+) beta
726	5902106	SRY (sex determining region Y)-box 20
727	5902110	SRY (sex determining region Y)-box 22; SRY (sex-determining region Y)-box 22
728	5924409	tight junction protein ZO-2 isoform C
729	6005717	ATPase e F0
730	6005772	putative G protein coupled receptor
731	6005938	utrophin; dystrophin-related protein
732	6005938	utrophin; dystrophin-related protein
733	6005948	WW domain-containing binding protein 4; formin binding protein 21
734	6010711	hereditary haemochromatosis protein precursor
735	6031192	phosphate carrier precursor isoform 1a; phosphate carrier, mitochondrial; phosphate carrier, mitochondrial precursor
736	6041669	ND B15
737	6094658	truncated form of cytochrome Bc1 J chain; similar to 1BGY
738	6175038	Son of sevenless protein homolog 2 (SOS-2)
739	6176530	alanine-glyoxylate aminotransferase homolog
740	6249687	R31155_1
741	6273778	trabeculin-alpha
742	6274550	ND B22 NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9 (22kD, B22)
743	6288790	beta-ureidopropionase
744	6330385	Unknown
745	6331429	Unknown
746	6382058	v-abl Abelson murine leukemia viral oncogene homolog 1 isoform b; Abelson murine leukemia viral (v-abl) oncogene homolog 1
747	6382071	diaphanous 2 isoform 12C; Diaphanous, Drosophila, homolog of, 2; diaphanous (Drosophila, homolog) 2

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
748	6433936	aczonin
749	6456828	phosphoglycerate kinase 1
750	6523797	adrenal gland protein AD-002
751	6572219	UCR ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide-like 1) dJ370M22.2 (
752	6580492	cN28H9.1 (novel protein)
753	6594629	pRGR2
754	6598323	GDP dissociation inhibitor 2; rab GDP-dissociation inhibitor, beta
755	6624122	3-hydroxyisobutyrate dehydrogenase
756	6631100	natural killer-tumor recognition sequence
757	6649914	growth/differentiation factor-11
758	6678455	transcription termination factor, RNA polymerase I
759	6681764	ND 39k NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 9 (39kD); NADH dehydrogenase (ubiquinone) Fe-S protein 2-like (NADH-coenzyme Q reductase)
760	6683124	Unknown
761	6686262	ZINC FINGER PROTEIN 36
762	6688130	poly-(ADP-ribose) polymerase II
763	6729803	Heat-Shock 70kd Protein 42kd Atpase N-Terminal Domain
764	6739500	LDLR-FUT fusion protein
765	6841066	calcium-binding transporter
766	6841110	Unknown
767	6841194	HSPC272
768	6841440	HSPC108
769	6841930	T cell receptor beta chain
770	6912238	peroxiredoxin 5; antioxidant enzyme B166
771	6912322	crumbs homolog 1; crumbs (Drosophila) homolog 1
772	6912396	glyoxylate reductase/hydroxypyruvate reductase
773	6912440	double-stranded RNA-binding zinc finger protein JAZ
774	6912482	LETM1 leucine zipper-EF-hand containing transmembrane protein 1
775	6912482	leucine zipper-EF-hand containing transmembrane protein 1
776	6912536	nicotinamide nucleotide transhydrogenase
777	6912536	nicotinamide nucleotide transhydrogenase
778	6912538	neurotensin receptor 2; neurotensin receptor, type 2
779	6912664	sirtuin 5, isoform 1; sir2-like 5; sirtuin type 5; sirtuin (silent mating type information regulation 2, S.cerevisiae, homolog) 5; silent mating type information regulation 2, S.cerevisiae, homolog 5
780	6912714	translocase of inner mitochondrial membrane 9 homolog (yeast); translocase of inner mitochondrial membrane 9 (yeast) homolog
781	6912714	translocase of inner mitochondrial membrane Tim9a
782	6996429	acetyl-coenzyme A synthethase (acetate-coA ligase)) dJ568C11.3 (novel AMP-binding enzyme similar to

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
783	6996429	novel AMP-binding enzyme similar to acetyl-coenzyme A synthethase (acetate-coA ligase)
784	7018398	hemopoietic cell kinase
785	7019351	cardiotrophin-like cytokine; neurotrophin-1/B-cell stimulating factor-3
786	7019545	secreted protein of unknown function
787	7020216	Unknown
788	7020807	mitochondrial ribosomal protein L22 , similar to
789	7022241	Unknown
790	7022343	Unknown
791	7022728	Unknown
792	7022751	Unknown
793	7242949	Unknown
794	7242979	Unknown
795	7243141	Unknown
796	7243219	Unknown
797	7243272	Unknown
798	7243280	Unknown
799	7245352	Hexokinase I With Glucose And Adp In The Active Site,Mutant Monomer Of Recombinant Human
800	7329718	Unknown
801	7430427	ionizing radiation resistance conferring protein - human
802	7431153	malate dehydrogenase (EC 1.1.1.37), cytosolic - human
803	7431833	NAD(P)+ transhydrogenase (B-specific) (EC 1.6.1.1) precursor, mitochondrial - human
804	7436377	plasma membrane Ca2+-ATPase variant 4a PMCA4a - human (fragment)
805	7439346	protein-tyrosine-phosphatase
806	7441369	tubulin beta chain - human
807	7447071	syntaxin
808	7447698	UDP glucuronosyltransferase (EC 2.4.1.-) 1A10 precursor - human
809	7452946	X-like 1 protein
810	7459551	Unknown
811	7487801	Unknown
812	7511895	Unknown
813	7512435	filamin, muscle
814	7512482	helicase II - human
815	7512482	helicase II - human gi|606833|gb|AAC50069.1| (U09820) helicase II
816	7512513	Unknown
817	7512598	Unknown
818	7512628	Unknown
819	7512754	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
820	7512754	Unknown
821	7512776	Unknown
822	7512977	Unknown
823	7513005	Unknown
824	7513021	Unknown
825	7513022	Unknown
826	7513076	Unknown
827	7513172	N-chimerin homolog F25965_3 - human
828	7513177	ND 14.1K NADH dehydrogenase (ubiquinone) (EC 1.6.5.3) 14.1K chain - human
829	7513178	ND acyl carrier NADH dehydrogenase (ubiquinone) (EC 1.6.5.3) acyl carrier chain, mitochondrial - human (fragment)
830	7513274	probable thyroid receptor interactor - human (fragment)
831	7513374	thrombospondin-p50 - human (fragment)
832	7524346	adenylate kinase 2 isoform b; Adenylate kinase-2, mitochondrial
833	7527760	Unknown
834	7582306	ALEX3 protein
835	7595299	opioid growth factor receptor
836	7643782	HDCMD47P
837	7656959	calpain 7; calpain like protease;
838	7656999	catenin
839	7657039	death receptor 6
840	7657050	hypothetical protein, estradiol-induced
841	7657257	translocase of outer mitochondrial membrane 20 (yeast) homolog
842	7657257	translocase of outer mitochondrial membrane 20homolog (TOM20)
843	7657343	metalloprotease 1 (pitrilysin family)
844	7657347	mitochondrial carrier homolog 2
845	7657347	mitochondrial carrier homolog 2
846	7657369	ND 19k NDUFA8
847	7657469	rat integral membrane glycoprotein POM121 , similar to
848	7657486	low molecular mass ubiquinone-binding protein
849	7657534	spastic ataxia of Charlevoix-Saguenay
850	7657554	soggy-1 gene; dickkopf-like 1 (soggy)
851	7657562	SH3-domain binding protein 4
852	7657581	solute carrier family 25, member 13 (citrin)
853	7657615	podocin
854	7661602	DKFZP564B167 protein
855	7661602	Unknown
856	7661678	RAS-related protein RAP1B; K-REV DKFZP586H0723 protein;
857	7661720	HIRA interacting protein 5; HIRIP5 protein; HIRA-interacting protein 5; HIRA-interacting protein 5
858	7661732	HSPC009 protein
859	7661732	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
860	7661800	HSPC141 protein
861	7661872	leucyl-tRNA synthetase, mitochondrial
862	7661872	leucyl-tRNA synthetase, mitochondrial; KIAA0028 protein
863	7661960	Rough Deal homolog, centromere/kinetochore protein; Rough Deal (Drosophila) homolog, centromere/kinetochore protein
864	7661996	Unknown
865	7662042	Rho guanine nucleotide exchange factor 10
866	7662046	Unknown
867	7662092	Unknown
868	7662168	Unknown
869	7662190	Unknown
870	7662190	Unknown
871	7662280	histone deacetylase 7B isoform HDRP; histone deacetylase 7; MEF-2 interacting transcription repressor (MITR) protein; histone deacetylase 7B
872	7662284	Unknown
873	7662314	Unknown
874	7662452	Unknown
875	7662470	neuroligin 1
876	7662480	Unknown
877	7662639	PTD011 protein
878	7662645	mitochondrial ribosomal protein S18B; mitochondrial ribosomal protein S18-2; mitochondrial 28S ribosomal protein S18-2
879	7662673	translocase of outer mitochondrial membrane 70 homolog A (yeast); translocase of outer mitochondrial membrane 70 (yeast) homolog A; KIAA0719 gene product
880	7662673	translocase of outer mitochondrial membrane 70homolog A
881	7669477	RNA-specific adenosine deaminase B1, isoform DRABA2b; RNA editase; human dsRNA adenosine deaminase DRADA2b
882	7669492	glyceraldehyde-3-phosphate dehydrogenase
883	7669520	neuregulin 1 isoform ndf43; heregulin, alpha (45kD, ERBB2 p185-activator); glial growth factor
884	7671629	KRAB box containing C2H2 type zinc finger protein
885	7671653	Unknown
886	7677070	silent information regulator 2 homolog
887	7678804	mitochondrial isoleucine tRNA synthetase
888	7705485	Unknown
889	7705501	Unknown
890	7705594	CGI-10 protein
891	7705616	CGI-112 protein
892	7705626	mitochondrial ribosomal protein S16
893	7705626	mitochondrial ribosomal protein S16; 28S ribosomal protein S16, mitochondrial

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
894	7705646	CGI-150 protein
895	7705704	glutathione S-transferase subunit 13 homolog mitochondrial
896	7705738	mitochondrial ribosomal protein S7; 30S ribosomal protein S7 homolog
897	7705797	CGI-87 protein
898	7705805	mitochondrial ribosomal protein S2
899	7705805	mitochondrial ribosomal protein S2
900	7705889	NEU1 protein
901	7705987	glycolipid transfer protein
902	7706057	mitochondrial ribosomal protein L27
903	7706073	GS15
904	7706117	peptide transporter 3; likely ortholog of rat peptide/histidine transporter 2
905	7706121	testicular haploid expressed gene
906	7706146	hBOIT for potent brain type organic ion transporter
907	7706154	NM23-H8
908	7706314	CGI-77 protein
909	7706349	mitochondrial ribosomal protein S33
910	7706449	fatty-acid-Coenzyme A ligase, long-chain 5; long-chain acyl-CoA synthetase 5; long-chain fatty acid coenzyme A ligase 5; FACL5 for fatty acid coenzyme A ligase 5
911	7706481	MO25 protein
912	7706549	CDC2-related protein kinase 7
913	7710129	LIM domain only 6
914	7770231	Unknown
915	7799988	large-conductance calcium-activated potassium channel beta
916	7959706	Unknown
917	7959889	Unknown
918	7959907	PRO2472
919	7981263	Unknown
920	8051579	adenylate kinase 3; Adenylate kinase-3, mitochondrial; GTP:AMP phosphotransferase
921	8131894	mitofilin
922	8216989	putative cell cycle control protein
923	8217423	bA108L7.7 (novel protein similar to C. elegans C25A1.13 (Tr:O02220))
924	8394499	ubiquitin associated protein
925	8488995	ND 20K NADH-ubiquinone oxidoreductase 20 kDa subunit, mitochondrial precursor (Complex I-20KD) (CI-20KD) (PSST subunit)
926	8570444	Contains similarity to an unnamed protein from Homo sapiens
927	8574030	diazepam binding inhibitor (GABA receptor modulator, acyl-Coenzyme A binding protein))) dJ1013A10.3 (related to DBI (

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
928	8574070	NFKB1
929	8671846	RNA adenosine deaminase gene, exon 15, Contains similarity to
930	8919645	T-cell receptor beta chain
931	8922081	Unknown
932	8922081	Unknown
933	8922275	Unknown
934	8922285	Unknown
935	8922307	Unknown
936	8922420	neuropilin and tolloid like-2
937	8922465	Unknown
938	8922511	mitochondrial ribosomal protein S18A
939	8922517	Unknown
940	8922569	Unknown
941	8922629	Unknown
942	8922665	Unknown
943	8922701	putative lipid kinase
944	8922742	Unknown
945	8922787	Unknown
946	8922804	Unknown
947	8922838	Unknown
948	8923001	Unknown
949	8923221	Unknown
950	8923291	Unknown
951	8923390	Unknown
952	8923390	Unknown
953	8923415	Unknown
954	8923417	Unknown
955	8923528	Unknown
956	8923870	hOAT4
957	8923930	uncharacterized hematopoietic stem/progenitor cells protein
958	8923930	uncharacterized hematopoietic stem/progenitor cells protein MDS0
959	8927581	testes-specific heterogenous nuclear ribonucleoprotein G-T
960	8928067	Malonyl-CoA decarboxylase, mitochondrial precursor (MCD)
961	9049352	3-methylcrotonyl-CoA carboxylase biotin-containing subunit
962	9256610	protocadherin beta 15 precursor
963	9257242	succinate dehydrogenase complex, subunit B, iron sulfur (Ip); iron-sulfur subunit
964	9296943	Cyclin T2
965	9297078	UBIQUINOL-CYTOCHROME C REDUCTASE COMPLEX 7.2 KDA PROTEIN
966	9367862	Unknown
967	9438229	phospholipase C beta 1
968	9501146	meiotic DNA transesterase/topoisomerase homolog isoform 2

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
969	9506437	FAPP1-associated protein 1
970	9506611	Unknown
971	9506611	Unknown
972	9506637	rab11-binding protein gi|7023581|dbj|BAA92015.1| (AK001978) unnamed protein product , similar to
973	9506697	Unknown
974	9506713	nucleolar protein family A, member 1; H/ACA small nucleolar RNPs protein 1
975	9506785	homeo box (H6 family) 1
976	9622528	NSAID-activated protein 1 NAG-1
977	9884738	AP-2 beta transcription factor
978	9910184	DC13 protein
979	9910244	mitochondrial ribosomal protein S22; gibt protein; chromosome 3 open reading frame 5; mitochondrial 28S ribosomal protein S22
980	9910280	UDP-glucose ceramide glucosyltransferase-like 1
981	9910382	mitochondrial import receptor Tom22
982	9910382	mitochondrial import receptor Tom22
983	9911130	protein phosphatase
984	9930803	A kinase (PRKA) anchor protein 7
985	9955433	Unknown
986	9966799	disrupter of silencing 10
987	9966893	CGI-203 protein
988	10047106	carboxypeptidase A3
989	10047118	G-protein gamma-12 subunit
990	10047120	insulin receptor tyrosine kinase substrate
991	10047167	Unknown
992	10047177	Unknown
993	10047183	Unknown
994	10047187	Unknown
995	10047199	Unknown
996	10047213	Unknown
997	10047231	Unknown
998	10047239	Unknown
999	10047243	Unknown
1000	10047247	Unknown
1001	10047249	Unknown
1002	10047277	Sarcolemmal-associated protein
1003	10047277	Unknown
1004	10047279	Unknown
1005	10047281	Unknown
1006	10047283	Unknown
1007	10047317	L-periaxin
1008	10047329	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1009	10047335	zinc finger protein
1010	10047341	Unknown
1011	10047341	Unknown
1012	10047347	Unknown
1013	10047361	Unknown
1014	10092604	HUG1 gene
1015	10092623	hematopoietic PBX-interacting protein gi|9930
1016	10092657	13kDa differentiation-associated protein; NADH: ubiquinone oxidoreductase
1017	10092657	ND B17.2
1018	10120604	L-3-Hydroxyacyl-Coa Dehydrogenase Complexed With Acetoacetyl-Coa And Nad+
1019	10179599	ND NDUFS2
1020	10179880	muscle-specific protein
1021	10181206	GABA(A) receptor-associated protein like 1
1022	10190653	sphingosine-1-phosphate lyase 1
1023	10190692	junctophilin 3; junctophilin type3 gi|9886738
1024	10241702	putative ZIC3 Binding protein from Xenopus laevis, similar to
1025	10241706	Unknown
1026	10257409	natural resistance-associated macrophage protein 1
1027	10257494	N-ethylmaleimide-sensitive factor
1028	10334442	hydroxysteroid (17-beta) dehydrogenase 7
1029	10334443	Unknown
1030	10334466	Unknown
1031	10337605	peroxisomal short-chain alcohol dehydrogenase
1032	10432782	testin
1033	10432971	Unknown
1034	10433147	poly(A) polymerase gamma; SRP RNA 3' adenylating enzyme/pap2
1035	10433320	huntingtin-associated protein
1036	10433905	Unknown
1037	10433929	Unknown
1038	10434023	Unknown
1039	10434055	Unknown
1040	10434106	Fanconi anemia complementation group D2 protein
1041	10434151	Unknown
1042	10434167	Unknown
1043	10434183	Unknown
1044	10434243	Unknown
1045	10434293	Unknown
1046	10434345	Unknown
1047	10434521	Unknown
1048	10434757	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1049	10434850	zinc finger protein 226
1050	10434904	Unknown
1051	10434988	Unknown
1052	10435007	Unknown
1053	10435244	Unknown
1054	10435551	Unknown
1055	10435767	Unknown
1056	10435899	Unknown
1057	10435947	Unknown
1058	10436007	Unknown
1059	10436258	Unknown
1060	10436263	Unknown
1061	10436325	Unknown
1062	10436604	Unknown
1063	10437144	Smac
1064	10437144	Unknown
1065	10437178	mitochondrial ribosomal protein L1
1066	10437189	Unknown
1067	10437384	M-phase phosphoprotein 1
1068	10437960	Unknown
1069	10437984	Unknown
1070	10438291	Unknown
1071	10438353	McKusick-Kaufman syndrome protein
1072	10438441	Unknown
1073	10438702	Unknown
1074	10438857	Unknown
1075	10438928	mitochondrial ribosomal protein S11
1076	10438968	Unknown
1077	10439079	Unknown
1078	10439244	Unknown
1079	10439312	Unknown
1080	10440252	bromodomain PHD finger transcription factor
1081	10440347	Unknown
1082	10440357	Unknown
1083	10440367	Unknown
1084	10440389	Unknown
1085	10440402	Unknown
1086	10440484	Unknown
1087	10441879	Unknown
1088	10441930	Unknown
1089	10443472	Rhesus blood group-associated glycoprotein (RH50A)
1090	10503988	Unknown
1091	10518340	muscleblind (Drosophila)-like

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1092	10567164	gene amplified in squamous cell carcinoma-1
1093	10639097	solute carrier family 24 (sodium/potassium/calcium exchanger), member 3) dJ122P22.1 (
1094	10645199	ADAM-TS disintegrin and metalloprotease with thrombospondin motifs-7 preproprotein; a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 7
1095	10716563	calnexin
1096	10719935	CELL DIVISION CYCLE 2-LIKE PROTEIN KINASE 5(CDC2-RELATED PROTEIN KINASE 5)
1097	10720290	SORTING NEXIN 14
1098	10720297	SYNAPTOJANIN 2 (SYNAPTIC INOSITOL-1,4,5-TRISPHOSPHATE 5-PHOSPHATASE 2)
1099	10720409	Zinc finger protein 294
1100	10764847	ND B18
1101	10798812	MLTK-alpha
1102	10834587	fer-1 like protein 3
1103	10834762	PNAS-102
1104	10834786	PNAS-117
1105	10834968	mannosidase, alpha B, lysosomal
1106	10835000	pancreatic lipase
1107	10835002	Rho GDP dissociation inhibitor (GDI) beta
1108	10835023	inositol 1,4,5-triphosphate receptor, type 1
1109	10835025	ND 24k
1110	10835045	retinaldehyde dehydrogenase 2
1111	10835057	N-acetyltransferase, homolog of S. cerevisiae ARD1; N-acetyltransferase ARD1, human homolog of
1112	10835059	farnesyltransferase, CAAX box, beta
1113	10835063	nucleophosmin (nucleolar phosphoprotein B23, numatrin)
1114	10835087	ND 10k
1115	10835089	neurofilament, heavy polypeptide (200kD); Neurofilament, heavy polypeptide
1116	10835109	myotubularin related protein 3; FYVE (Fab1 YGLO23 Vsp27 EEA1 domain) dual-specificity protein phosphatase
1117	10835155	tumor necrosis factor (cachectin)
1118	10835165	CD59 antigen p18-20
1119	10835173	nitric oxide synthase 1
1120	10835189	glutathione reductase
1121	10835220	ATPase, Ca++ transporting, fast twitch 1
1122	10863907	hepatocellular carcinoma associated protein; breast cancer
1123	10863927	peptidylprolyl isomerase A
1124	10863945	ATP-dependant DNA helicase II
1125	10863985	G4 protein
1126	10864011	CGI-44 protein; sulfide dehydrogenase like (yeast)

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1127	10864043	kidney and liver proline oxidase 1
1128	10864077	calcium channel, voltage-dependent, alpha 1H subunit
1129	10945428	membrane-associated guanylate kinase MAGI3
1130	11024710	Unknown
1131	11024714	ubiquitin B
1132	11034855	Unknown
1133	11038674	CD79B antigen, isoform 1 precursor; B-cell-specific glycoprotein B29
1134	11055998	guanine nucleotide binding protein beta subunit 4 [Homo sapi
1135	11056030	protocadherin gamma subfamily A, 2, isoform 1 precursor
1136	11066958	mutant beta-globin
1137	11066968	EH domain-containing protein FKSG7
1138	11095436	valosin-containing protein
1139	11096171	RNA polymerase III transcription initiation factor B
1140	11121497	Trp4-associated protein TAP1, similar to
1141	11127695	SYT/SSX4 fusion protein
1142	11128019	cytochrome c
1143	11128031	protocadherin gamma subfamily B, 5, isoform 1 precursor
1144	11139093	GrpE-like protein cochaperone
1145	11141885	carrier family 5 (choline transporter), member 7
1146	11141891	ERGL protein
1147	11177148	mitochondrial ribosomal protein L12
1148	11177148	mitoribosomal protein L12
1149	11225260	DNA TOPOISOMERASE I
1150	11225266	transient receptor potential cation channel, subfamily M, member 5; MLSN1- and TRP-related; MLSN1 and TRP-related
1151	11245229	ninein-Lm isoform
1152	11252721	glutaryl-CoA dehydrogenase
1153	11252721	glutaryl-CoA dehydrogenase (EC 1.3.99.7) [imported] - human
1154	11267525	probable RNA helicase
1155	11275568	mucin 5B
1156	11275986	glycerol-3-phosphate dehydrogenase 3
1157	11276083	fatty-acid-Coenzyme A ligase, long-chain 2
1158	11276083	long-chain fatty-acid-Coenzyme A ligase 2; acyl-activating enzyme; acyl-CoA synthetase; fatty acid thiokinase (long-chain); lignoceroyl-CoA synthase; long-chain acyl-CoA synthetase 2
1159	11276655	ribosomal protein S26 [imported] - human
1160	11276938	villin 2
1161	11277141	heat shock 90kD protein beta
1162	11280538	Unknown
1163	11280677	Unknown
1164	11281511	Unknown
1165	11321341	MondoA

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1166	11321569	olfactory receptor, family 3, subfamily A, member 2
1167	11321571	slit homolog 3 (Drosophila); slit (Drosophila) homolog 3; slit (Drosophila) homolog 2; slit2
1168	11321579	myosin, heavy polypeptide 13, skeletal muscle; extraocular muscle myosin heavy chain
1169	11321581	succinyl-CoA synthetase alpha subunit
1170	11321583	succinate-CoA ligase, ADP-forming, beta subunit
1171	11321613	epilepsy, progressive myoclonus type 2, Lafora disease (laforin)
1172	11321615	T-box 3 protein; T-box 3; T-box transcription factor TBX3
1173	11323320	ubiquitin-conjugating enzyme E2 variant 1 (isoform 2, similar to variant 2 (UBE2V2, MMS2)
1174	11342570	metalloproteinase 24 (membrane-inserted), matrix
1175	11342672	myosin, heavy polypeptide 3, skeletal muscle, embryonic
1176	11345448	lipopolysaccharide-binding protein
1177	11345456	fibroblast growth factor receptor-like 1 precursor
1178	11345478	Unknown
1179	11345539	novel Helicase C-terminal domain
1180	11359874	GTP-binding protein 2
1181	11359883	Unknown
1182	11359946	leucine zipper-EF-hand containing transmembrane protein 1
1183	11359985	Unknown
1184	11359986	Unknown
1185	11360009	Bcl-Rambo
1186	11360009	Unknown
1187	11360063	matrilin 2 precursor
1188	11360067	Unknown
1189	11360079	Unknown
1190	11360112	Unknown
1191	11360155	Unknown
1192	11360155	Unknown
1193	11360156	Unknown
1194	11360162	Unknown
1195	11360185	Unknown
1196	11360188	Unknown
1197	11360228	Unknown
1198	11360250	Unknown
1199	11360251	Unknown
1200	11360294	Unknown
1201	11360310	myosin VIIa, long form - human
1202	11360321	properdin
1203	11374664	isocitrate dehydrogenase (EC 1.1.1.42), cytosolic
1204	11385354	polybromo 1
1205	11385644	CTCL tumor antigen se2-1

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1206	11385664	CTCL tumor antigen se89-1
1207	11386147	prosaposin
1208	11399466	D-2-hydroxy-acid dehydrogenase
1209	11415024	diacylglycerol kinase, alpha (80kD)
1210	11416393	mitochondrial ribosomal protein L22
1211	11416669	nicotinamide nucleotide transhydrogenase
1212	11417363	low molecular mass ubiquinone-binding protein
1213	11417363	low molecular mass ubiquinone-binding protein
1214	11418549	eyes absent (Drosophila) homolog 4
1215	11418714	Unknown
1216	11419832	phosphorylase kinase, alpha 1
1217	11421027	Unknown
1218	11422272	ribosomal protein S6 kinase, 90kD
1219	11423142	basic leucine zipper nuclear factor 1
1220	11423880	alpha-SNAP
1221	11424404	mitochondrial ribosomal protein S23
1222	11424724	neurofilament 3
1223	11425565	Unknown
1224	11425836	low density lipoprotein receptor-related protein 3
1225	11427613	Unknown
1226	11427636	GTPase Rab14
1227	11428230	aldehyde dehydrogenase 1 family, member B1
1228	11429803	Unknown
1229	11430299	hexokinase 1
1230	11431667	multiple inositol polyphosphate phosphatase 2
1231	11432018	Unknown
1232	11432441	Unknown
1233	11432489	general transcription factor IIE, polypeptide 1 (alpha subunit, 56kD)
1234	11433007	peroxisomal enoyl-coenzyme A hydratase-like protein
1235	11433596	tryptophanyl-tRNA synthetase
1236	11434079	Unknown
1237	11434447	Unknown
1238	11434986	COQ6_HUMAN PUTATIVE UBIQUINONE BIOSYNTHESIS MONOOXGENASE COQ
1239	11435257	Unknown
1240	11435724	mannosidase, beta A, lysosomal
1241	11436135	RAS-RELATED PROTEIN R-RAS2
1242	11436533	aldehyde dehydrogenase 2 family (mitochondrial)
1243	11436778	inositol polyphosphate-4-phosphatase, type II, 105kD
1244	11437205	Unknown
1245	11440003	transgelin
1246	11441230	skeletal muscle specific actinin, alpha 3
1247	11493459	PRO2619

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1248	11493489	PRO2620
1249	11493522	Unknown
1250	11493552	Unknown
1251	11496882	ELK4 protein, isoform b; ETS-domain protein; SRF accessory protein 1
1252	11497601	metallaproteinase-disintegrin
1253	11526149	ATPase CF6 F0
1254	11526456	frataxin
1255	11526471	tripartite motif protein TRIM14 isoform alpha
1256	11526573	heat shock cognate protein 54
1257	11526789	inorganic pyrophosphatase 2
1258	11545761	potassium channel, subfamily K, member 12; tandem pore domain potassium channel THIK-2
1259	11545847	basic-helix-loop-helix-PAS protein
1260	11545863	methylcrotonoyl-Coenzyme A carboxylase 2
1261	11545869	popeye protein 2
1262	11545894	RFamide-related peptide precursor
1263	11559927	mitochondrial ribosomal protein S14
1264	11596402	MAGE-D4
1265	11596859	mitochondrial ribosomal protein L17
1266	11602741	complement component 8, alpha polypeptide
1267	11602963	heparan sulfate proteoglycan perlecan
1268	11611734	GREB1a
1269	11612659	FXYD domain-containing ion transport regulator 7
1270	11612670	phospholemman, isoform b precursor; FXYD domain-containing
1271	11640566	hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-Coenzyme A hydratase beta
1272	11640578	glyoxylate reductase/hydroxypyruvate reductase
1273	11641249	protein kinase Njmu-R1
1274	11641283	LIM homeobox protein 5
1275	11641413	cell division cycle 25B, isoform 3; CDC25B
1276	11761696	bHLHZip transcription factor BIGMAX gamma
1277	11863673	guanine nucleotide binding protein (G protein), alpha stimulating activity polypeptide 1) dJ309F20.1.5 (isoform 5 of
1278	11890755	RNA helicase II/Gu protein
1279	11907570	mutant desmin
1280	11908171	Fas-binding protein Daxx
1281	11935053	sarcolemmal associated protein 1
1282	11968003	5-azacytidine induced gene 2, similar to
1283	11968152	somatostatin receptor-interacting protein
1284	11990879	phosphoglycerate kinase 2
1285	11991867	odorant receptor HOR3'beta5
1286	12001946	My003 protein

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1287	12001986	My022 protein
1288	12001992	brain my025
1289	12002038	brain my045 protein
1290	12002042	brain my048 protein
1291	12002201	serine/threonine protein kinase PFTAIRE-1
1292	12003293	organic anion transporter 2
1293	12005493	NPD011
1294	12005918	GRIM19
1295	12006049	EF1a-like protein
1296	12006205	TNFIP-iso
1297	12038977	Unknown
1298	12043738	thioredoxin reductase, mitochondrial
1299	12052810	Unknown
1300	12052820	COQ7 protein; timing protein; ubiquinone biosynthesis protein
1301	12052826	RAB-8b protein,small GTP-binding protein
1302	12052828	Unknown
1303	12052872	Unknown
1304	12052908	Unknown
1305	12052971	methyltransferase COQ3
1306	12052989	Unknown
1307	12052991	Unknown
1308	12053107	Unknown
1309	12053245	Unknown
1310	12053255	Unknown
1311	12060822	serologically defined breast cancer antigen NY-BR-16
1312	12060832	serologically defined breast cancer antigen NY-BR-40
1313	12061185	ASC-1 complex subunit P200
1314	12081909	semaphorin Y
1315	12214171	putative small GTP-binding protein (rab1b)
1316	12214288	dJ402H5.2 (novel protein similar to worm and fly proteins)
1317	12230015	CYTOCHROME B5 OUTER MITOCHONDRIAL MEMBRANE ISOFORM PRECURSOR
1318	12230075	GLYCEROL KINASE, TESTIS SPECIFIC 1
1319	12232373	rab6 GTPase activating protein (GAP and centrosome-associated)
1320	12232421	tricarboxylate carrier protein
1321	12232477	Unknown
1322	12239360	LYST-interacting protein LIP6
1323	12246901	tumor protein D52-like 2
1324	12248755	mono ATP-binding cassette protein
1325	12314005	Unknown
1326	12314016	transcription factor TFIIS , similar to
1327	12314029	proteasome subunit 7
1328	12314062	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1329	12314123	uncharacterized hematopoietic stem/progenitor cells protein MDS030 (8923932)
1330	12314190	dJ445H2.2 (novel protein)
1331	12314195	Unknown
1332	12328445	NPAS3
1333	12382773	caspase recruitment domain protein 11
1334	12382789	OSBP-related protein 7; ORP7
1335	12383092	Unknown
1336	12407403	tripartite motif protein TRIM9 isoform alpha
1337	12408656	calpain 1, large subunit
1338	12597655	kinetochore protein
1339	12620194	Unknown
1340	12620246	CD36
1341	12620252	CD36
1342	12620871	phosphoinositide-3-kinase gamma catalytic subunit
1343	12621903	cathepsin S
1344	12643256	pilin-like transcription factor
1345	12643326	CIP1-INTERACTING ZINC FINGER PROTEIN (NUCLEAR PROTEIN NP94)
1346	12643329	CGI-51
1347	12643417	Pyruvate dehydrogenase protein X component, mitochondrial precursor (Dihydrolipoamide dehydrogenase-binding protein of pyruvate dehydrogenase complex) (E3-binding protein) (E3BP) (proX)
1348	12643637	ADAM-TS 4 PRECURSOR (A DISINTEGRIN AND METALLOPROTEINASE WITH THROMBOSPONDIN MOTIFS 4)
1349	12643716	PROTEIN TYROSINE PHOSPHATASE, NON-RECEPTOR TYPE 13
1350	12643796	RETINOBLASTOMA-BINDING PROTEIN 8
1351	12643896	Zinc finger protein 236
1352	12644018	AF-6 PROTEIN
1353	12644090	T-BOX TRANSCRIPTION FACTOR TBX18
1354	12644310	COATOMER BETA SUBUNIT(BETA-COP)
1355	12644370	Zinc finger X-linked protein ZXDB
1356	12652715	nucleolar GTPase
1357	12652761	Unknown
1358	12652763	Unknown
1359	12652773	Unknown
1360	12652981	glycogen synthase kinase 3 beta
1361	12652989	Unknown
1362	12653017	LRP16 protein
1363	12653371	phosphoglycerate mutase 1
1364	12653507	aspartate transaminase 2

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1365	12653549	mitochondrial ribosomal protein S6
1366	12653687	Unknown
1367	12653775	helicase-like protein NHL
1368	12653827	mitochondrial carrier homolog 1 or presenilin-associated protein
1369	12653855	dynamitin
1370	12654077	NICE-5 protein
1371	12654149	Unknown
1372	12654285	peptide N-glycanase homolog
1373	12654289	transcription termination factor, mitochondrial
1374	12654333	HCDI protein
1375	12654407	N-Acetylglucosamine kinase
1376	12654521	Unknown
1377	12654627	metalloprotease 1
1378	12654675	transcobalamin II; macrocytic anemia
1379	12655133	CGI-63 protein , similar to
1380	12655157	centrosomal protein 2
1381	12655195	heat shock 75 protein
1382	12656979	antigen, T-cell receptor
1383	12657106	Unknown
1384	12659007	protein kinase D2
1385	12669909	long-chain fatty-acid-Coenzyme A ligase 4, isoform 2; long-chain acyl-CoA synthetase 4; acyl-activating enzyme
1386	12697312	putative chromatin modulator
1387	12697482	novel zinc finger protein similar to rat RIN ZF)
1388	12697776	polyadenylation specificity factor
1389	12697899	Unknown
1390	12697903	Unknown
1391	12697947	Unknown
1392	12697951	Unknown
1393	12697957	Unknown
1394	12697983	Unknown
1395	12697991	Unknown
1396	12697995	Unknown
1397	12698037	Unknown
1398	12698043	Unknown
1399	12698057	likley ortholog of rat CPG2 protein
1400	12698069	Unknown
1401	12698075	Unknown
1402	12700223	recombination activating protein 1
1403	12707570	enoyl Coenzyme A hydratase, short chain, 1, mitochondrial
1404	12711660	protein kinase, lysine deficient 1
1405	12711664	Unknown
1406	12711674	yeast Upf3, variant B, similar to

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1407	12725813	poly(ADP-ribosyl)transferase
1408	12729652	cell adhesion molecule with homology to L1CAM (close homologue of L1)
1409	12733033	caldesmon 1 or) NAG22 protein
1410	12733091	replication initiation region protein (60kD)
1411	12734392	annexin A13
1412	12734816	PRP4/STK/WD splicing factor
1413	12735217	surfeit 5
1414	12735226	adenylate kinase 3 alpha
1415	12735430	PKCq-interacting protein PICOT
1416	12738042	klotho
1417	12738974	Unknown
1418	12740808	A kinase anchor protein 10
1419	12741202	UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase
1420	12741866	protein expressed in thyroid, similar to
1421	12742008	chondroitin sulfate proteoglycan 3
1422	12742415	complement component C1q receptor
1423	12751117	PNAS-140
1424	12751119	PNAS-141
1425	12751452	PDZ domain-containing protein AIPC
1426	12803243	Unknown
1427	12803281	VDAC-3
1428	12803349	transcription factor 19, similar to
1429	12803387	antiquitin 1
1430	12803567	transgelin 2
1431	12803843	protein kinase, cAMP-dependent, regulatory, type II, alpha, similar to
1432	12803855	metastasis suppressor protein
1433	12803915	glucosidase I , similar to
1434	12804041	nuclear protein E3-3 orf1
1435	12804069	FK506-binding protein 4 (59kD) , similar to
1436	12804185	colon cancer-associated protein Mic1, similar to
1437	12804225	Unknown
1438	12804313	expressed sequence 2 embryonic lethal , similar to
1439	12804319	carbonyl reductase
1440	12804667	Unknown
1441	12804743	Unknown
1442	12804755	NPD002 protein , similar to
1443	12804821	Unknown
1444	12804897	branched chain aminotransferase 2, mitochondrial, similar to
1445	12804901	isocitrate dehydrogenase 3 gamma
1446	12805021	acyl-Coenzyme A dehydrogenase family, member 8
1447	12805031	roundabouth

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1448	12830367	serine/threonine kinase 33
1449	12862320	WDC146
1450	12963353	fenestrated-endothelial linked structure protein
1451	13027604	mitochondrial ribosomal protein S34
1452	13027608	Unknown
1453	13027640	lysine-ketoglutarate reductase /saccharopine dehydrogenase
1454	13095054	ovarian immunoreactive antigen
1455	13096727	Smac Bound To Xiap-Bir3 Domain
1456	13096755	Ras G12v - Pi 3-Kinase Gamma Complex
1457	13097156	ND 39k
1458	13097243	Unknown
1459	13097693	Unknown
1460	13111705	Carnitine O-acetyltransferase (Carnitine acetylase) (CAT)
1461	13111762	solute carrier family 19 (folate transporter), member 1 , similar to
1462	13112023	coenzyme Q, 7homolog
1463	13123976	ARGININE-TRNA-PROTEIN TRANSFERASE 1
1464	13124237	F-box only protein 10
1465	13124883	HsKin17 protein
1466	13128992	Unknown
1467	13128998	Unknown
1468	13129014	Unknown
1469	13129080	Unknown
1470	13129092	Unknown
1471	13129144	Unknown
1472	13161081	testis protein
1473	13177634	surfactant protein B-binding protein
1474	13177648	EGF factor 8 protein
1475	13177700	Unknown
1476	13184052	butyrophilin, subfamily 2, member A3
1477	13194197	kinesin family member 13B; guanylate kinase associated kinesin
1478	13194522	PMF-1 binding protein
1479	13236495	quinone oxidoreductase; NADPH
1480	13236559	Unknown
1481	13242069	nuclear transcription factor NFX2
1482	13242172	potassium voltage-gated channel, Shab-related subfamily, member 2
1483	13242739	myelin P2 protein
1484	13249985	Lowe oculocerebrorenal syndrome protein
1485	13259127	cullin CUL4B
1486	13259497	retinoblastoma-binding protein 1, isoform I
1487	13272567	ND 5
1488	13272568	ND 6
1489	13272595	ND 5 NADH dehydrogenase subunit 5

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1490	13272697	ND 1 NADH dehydrogenase subunit 1
1491	13272855	ATPase 8
1492	13273190	cox 2
1493	13274124	Unknown
1494	13276227	chromogranin B(isoform 2)
1495	13276598	Unknown
1496	13276617	Unknown
1497	13278690	Unknown
1498	13324710	interleukin 3 receptor, alpha (low affinity); Interleukin-3
1499	13325066	cadherin EGF LAG seven-pass G-type receptor 3; EGF-like-domain
1500	13325162	Unknown
1501	13325394	phosphatidylserine synthase 1, similar to
1502	13359201	Unknown
1503	13375614	peroxisomal long-chain acyl-coA thioesterase
1504	13375634	human immunodeficiency virus type I enhancer-binding protein
1505	13375744	Unknown
1506	13375809	Unknown
1507	13375817	Unknown
1508	13375838	Unknown
1509	13375872	Unknown
1510	13375932	Unknown
1511	13375940	Unknown
1512	13375942	Unknown
1513	13376007	Unknown
1514	13376011	engulfment and cell motility 3; ced-12 homolog 3
1515	13376021	Unknown
1516	13376038	Unknown
1517	13376052	Unknown
1518	13376093	Unknown
1519	13376107	Unknown
1520	13376144	Unknown
1521	13376284	Unknown
1522	13376331	Unknown
1523	13376437	Unknown
1524	13376445	Unknown
1525	13376490	Unknown
1526	13376580	Unknown
1527	13376617	Unknown
1528	13376640	putative N-acetyltransferase
1529	13376662	Unknown
1530	13376717	Unknown
1531	13376741	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1532	13376747	Unknown
1533	13376749	Unknown
1534	13376776	Unknown
1535	13376812	type 1 protein phosphatase inhibitor
1536	13376826	UL16-binding protein 1
1537	13376854	UBX domain-containing 1; UBX domain-containing 2
1538	13376991	voltage-dependent calcium channel beta 2 subunit
1539	13386494	Unknown
1540	13399777	Macrophage Migration Inhibitory Factor (Mif) Complexed With Inhibitor.
1541	13431759	PARAPLEGIN
1542	13431763	Pre-mRNA cleavage complex II protein Pcf11
1543	13435131	WW domain-containing binding protein 4
1544	13435350	ferredoxin reductase isoform 1
1545	13436080	cleft lip and palate associated transmembrane protein 1
1546	13436188	mitochondrial ribosomal protein S2
1547	13436197	Unknown
1548	13436275	LON PROTEASE HOMOLOG, MITOCHONDRIAL PRECURSOR
1549	13436296	Unknown
1550	13436308	Unknown
1551	13436335	IF-1 ATPase inhibitor precursor
1552	13436395	Unknown
1553	13436413	glucose phosphate isomerase
1554	13445577	EDAG
1555	13449263	Unknown
1556	13449269	Unknown
1557	13469731	breast cancer antigen NY-BR-1.1
1558	13470094	apolipoprotein L, 5
1559	13477253	Unknown
1560	13487904	Unknown
1561	13489087	serine (or cysteine) proteinase inhibitor, clade B (ovalbumin), member 1; protease inhibitor 2 (anti-elastase)
1562	13489095	sialoadhesin precursor; sialic acid-binding immunoglobulin-like lectin 1
1563	13491972	liver nuclear protein
1564	13507059	ubiquitin protein ligase
1565	13509322	suppression of tumorigenicity 5
1566	13514831	DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 10, ATP-dependent RNA helicase
1567	13516379	aldehyde oxidase 1
1568	13518228	methylcrotonoyl-Coenzyme A carboxylase
1569	13528660	ribosomal protein L4, similar to
1570	13528960	ND 18k

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1571	13529047	transforming growth factor, alpha
1572	13529221	PTD017 protein
1573	13529257	aldo-keto reductase family 1, member B1
1574	13537192	SCCA1b
1575	13540475	serum amyloid A2
1576	13540477	wingless-type MMTV integration site family, member 3 precursor
1577	13540574	Unknown
1578	13540576	Unknown
1579	13540590	C/EBP-induced protein
1580	13540606	suppressor of potassium transport defect 3 g
1581	13543342	Unknown
1582	13543446	Unknown
1583	13543618	ATPase B F0
1584	13543706	Unknown
1585	13543933	Unknown
1586	13544007	Unknown
1587	13544072	glycerol-3-phosphate dehydrogenase 1 (soluble), similarity to
1588	13559241	Unknown
1589	13559363	mitochondrial ribosomal protein L9
1590	13559404	mitochondrial ribosomal protein L43
1591	13560110	Unknown
1592	13569848	cell cycle progression 2 protein
1593	13569913	exonuclease NEF-sp
1594	13569930	toll-like receptor 10
1595	13569948	Unknown
1596	13569962	small GTP-binding protein
1597	13591536	Unknown
1598	13606056	DNA dependent protein kinase catalytic subunit
1599	13620885	mitochondrial ribosomal protein S6
1600	13623251	transcription factor EB , similar to
1601	13623369	Unknown
1602	13623465	peroxisomal long-chain acyl-coA thioesterase
1603	13623483	lysosomal-associated membrane protein 1
1604	13623595	DNA segment on chromosome 191177 expressed sequence
1605	13623615	Unknown
1606	13623617	Unknown
1607	13623635	Unknown
1608	13623689	Unknown
1609	13623693	Unknown
1610	13626125	ADAM-TS-9 precursor (A disintegrin and metalloproteinase with thrombospondin motifs 9) (ADAM-TS 9) (ADAM-TS9)
1611	13627233	aldo-keto reductase family 7, member A3
1612	13627252	oxoglutarate dehydrogenase

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1613	13627389	elongation factor-2 kinase
1614	13627804	acyl-Coenzyme A dehydrogenase, short/branched chain precursor
1615	13628614	Na,K-ATPase subunit alpha 2
1616	13628881	Unknown
1617	13629150	cox 4
1618	13630128	faciogenital dysplasia protein
1619	13630492	Unknown
1620	13630567	Unknown
1621	13630862	aldehyde dehydrogenase 5 family, member A1
1622	13630871	Unknown
1623	13630873	protein kinase, cAMP-dependent, regulatory, type II, beta
1624	13631242	reelin
1625	13631440	PEROXIREDOXIN 2
1626	13631521	mitochondrial ribosomal protein S7
1627	13631678	UCR 5
1628	13631907	mitogen-activated protein kinase kinase kinase kinase 1
1629	13632179	myosin, heavy polypeptide 13, skeletal muscle
1630	13632266	thyroid hormone receptor interactor 2; PPARG binding protein
1631	13632616	carrier ANT2
1632	13632896	phosphoglucomutase 1
1633	13633168	plastin 3 precursor
1634	13633370	Notchhomolog 3
1635	13635754	CTCL tumor antigen se1-1
1636	13635919	Unknown (now 4507953)
1637	13636042	Unknown
1638	13636047	3-hydroxyisobutyryl-Coenzyme A hydrolase
1639	13636157	Unknown
1640	13636168	eukaryotic translation elongation factor 1 beta 2
1641	13636504	interferon-induced protein 75, 52kD
1642	13636598	Unknown
1643	13637083	Unknown
1644	13637529	Unknown
1645	13637537	ETAA16 protein
1646	13637608	ND 75K
1647	13637631	VDAC-2 voltage-dependent anion channel 2 (H. sapiens) , similar to
1648	13637711	glycine cleavage system protein H (aminomethyl carrier) (H. sapiens) , similar to
1649	13637735	Unknown
1650	13637796	Unknown
1651	13637833	cox 7a like, COX7RP (cytochrome c oxidase subunit VII-related protein), estrogen receptor binding CpG island
1652	13637948	glutathione S-transferase M5

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1653	13638591	Unknown
1654	13638758	Unknown
1655	13639105	Unknown
1656	13639114	succinate dehydrogenase, Ip
1657	13639187	Unknown
1658	13639470	Unknown
1659	13639628	acetyl-Coenzyme A acetyltransferase 1 (acetoacetyl Coenzyme A thiolase), mitochondrial
1660	13639817	malic enzyme 3, NADP(+)-dependent, mitochondrial
1661	13640712	phosphoinositide-3-kinase, class 2, alpha polypeptide
1662	13640950	interleukin 11 receptor, alpha
1663	13641918	sirtuin 3
1664	13643253	kinesin family member 3A
1665	13643321	Unknown
1666	13643514	Unknown
1667	13643534	ribosomal protein L12; 60S ribosomal protein L12 (H. sapiens) , similar to
1668	13643564	exostoses1
1669	13643652	flavohemoprotein b5+b5R
1670	13643704	protein tyrosine phosphatase,receptor type
1671	13644108	proteasome 26S subunit, non-ATPase, 1
1672	13644418	Unknown
1673	13644786	butyrophilin, subfamily 1, member A1
1674	13645381	HLA-B associated transcript 2 (H. sapiens) , similar to
1675	13645492	heat shock 70kD protein-like 1
1676	13645618	dihydropyrimidinase related protein-3
1677	13646385	creatine kinase, sarcomeric mitochondrial
1678	13646774	quinoid dihydropteridine reductase
1679	13647276	L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain
1680	13647558	carrier ANT1
1681	13647920	gamma-glutamyltransferase 1
1682	13647960	tumor necrosis factor, alpha-induced protein 2
1683	13648234	Unknown
1684	13648426	cox assembly protein isoform 2
1685	13648611	serine/threonine kinase 2
1686	13648964	alanyl-tRNA synthetase
1687	13649010	odzhomolog 1
1688	13649058	Unknown
1689	13649119	SEX gene
1690	13649217	VDAC-1
1691	13649475	Unknown
1692	13649658	UCR ubiquinol-cytochrome c reductase binding protein
1693	13650446	heat shock 70kD protein 2

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1694	13650574	glutamate dehydrogenase 2 mitochondrial precursor
1695	13650639	melanoma antigen, family B, 1
1696	13650785	spectrin, beta, non-erythrocytic 5
1697	13650793	elongation factor SIII p15 subunit
1698	13650874	putative receptor protein
1699	13650942	Unknown
1700	13650992	Unknown
1701	13651038	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 4
1702	13651229	Rho GTPase activating protein 6 isoform 4
1703	13651413	Fc fragment of IgG binding protein (H. sapiens) , similar to
1704	13651526	androgen-induced prostate proliferative shutoff associated protein
1705	13651706	golgin-like protein
1706	13651985	type 1 RNA helicase pNORF1 or nonsense-mediated mRNA decay trans-acting factor
1707	13652204	Unknown
1708	13652240	ribosomal protein S7
1709	13652246	ARF protein
1710	13652324	ras-related small GTPasehypothetical protein X
1711	13652801	Rap1 guanine-nucleotide-exchange factor directly activated by cA
1712	13653049	acyl-Coenzyme A dehydrogenase, C-2 to C-3 short chain precursor
1713	13653910	carboxypeptidase D precursor
1714	13654274	Unknown
1715	13654278	Unknown
1716	13654294	Unknown
1717	13654678	Unknown
1718	13654685	ATP-binding cassette, sub-family C, member 1, isoform 6
1719	13655145	UCR ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide-like 1
1720	13655148	EH-domain containing 2; EH domain containing 2 , similar to
1721	13655297	Unknown
1722	13676336	Unknown
1723	13676857	heat shock 70kD protein 2; Heat-shock 70kD protein-2
1724	13699811	WHSC1L1 protein isoform long; Wolf-Hirschhorn syndrome candidate 1-like 1 protein
1725	13751974	Unknown
1726	13774961	autoimmune infertility-related protein
1727	13775158	Unknown
1728	13775166	Unknown
1729	13775186	ring finger protein 17 isoform long
1730	13775208	Unknown
1731	13775210	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1732	13775216	Unknown
1733	13775232	Unknown
1734	13784938	Unknown
1735	13786129	RAS-RELATED PROTEIN RAB-33B
1736	13786847	L-Lactate Dehydrogenase H Chain, Ternary Complex With Nadh And Oxamate
1737	13787197	DEAD/Hbox polypeptide 11
1738	13787215	sirtuin 5, isoform 2
1739	13787217	FAT tumor suppressor 2 precursor; multiple epidermal growth factor-like domains 1; cadherin family member 8
1740	13794267	RAB7, member RAS oncogene family; Ras-associated protein RAB
1741	13872241	ligand of numb-protein X
1742	13874437	cerebral protein-11
1743	13876386	epiplakin 1
1744	13899231	mitochondrial ribosomal protein L9
1745	13899275	Unknown
1746	13929460	PTH-responsive osteosarcoma B1 protein
1747	13929467	chemokine binding protein 2
1748	13937401	Unknown
1749	13937769	RIKEN cDNA 1200013F24 gene , similar to
1750	13937888	heterogeneous nuclear ribonucleoprotein C
1751	13938170	Unknown
1752	13938215	taxol resistant associated protein
1753	13938297	heat shock cognate 71-kd protein, similar to
1754	13938442	neuronal protein, mitochondrial Complex I subunit
1755	13938539	cyclin D binding Myb-like transcription factor 1
1756	13938571	Unknown
1757	13938593	Unknown
1758	13938619	creatine kinase, muscle
1759	13994164	Charcot-Marie-Tooth duplicated region transcript 1
1760	13994188	AKAP-associated sperm protein
1761	13994259	mitochondrial ribosomal protein S5
1762	13994280	complement-c1q tumor necrosis factor-related protein 7+F792
1763	13994325	putative b,b-carotene-9',10'-dioxygenase
1764	14017783	Unknown
1765	14017783	Unknown
1766	14017807	Unknown
1767	14017833	Unknown
1768	14017865	Unknown
1769	14017899	Unknown
1770	14017903	Unknown
1771	14017903	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1772	14017923	Unknown
1773	14017941	Unknown
1774	14017943	Unknown
1775	14017949	Unknown
1776	14017957	Unknown
1777	14017971	Unknown
1778	14028389	mitochondrial ribosomal protein L41
1779	14028403	mitochondrial ribosomal protein S28
1780	14028405	mitochondrial ribosomal protein S29
1781	14028875	UDP-glucuronic acid/UDP-N-acetylgalactosamine dual transporter; KIAA0260 protein; UDP-glucuronic acid/UDP-N-acetylgalactosamine dual transporter
1782	14028877	mitochondrial ribosomal protein S25; mitochondrial 28S ribosomal protein S25
1783	14041699	ESTRADIOL 17 BETA-DEHYDROGENASE 8
1784	14041874	MAPKK like protein kinase /PDZ-binding kinase
1785	14041889	Unknown
1786	14041976	Unknown
1787	14041978	CDA02 protein
1788	14041989	Unknown
1789	14042018	Unknown
1790	14042066	Unknown
1791	14042110	Unknown
1792	14042216	Unknown
1793	14042323	Unknown
1794	14042336	Unknown
1795	14042441	Unknown
1796	14042814	Unknown
1797	14042822	Unknown
1798	14042850	Unknown
1799	14042923	chromosome 9 open reading frame 5
1800	14043187	aldehyde dehydrogenase 4 A1
1801	14043217	plectin 1, intermediate filament bindi
1802	14043281	leucine-rich neuronal protein
1803	14043412	Unknown
1804	14043451	succinyl-CoA synthetase beta subunit GTP-specific
1805	14043654	phosphofructokinase, muscle, similar to
1806	14043666	Unknown
1807	14043738	Unknown
1808	14124942	ribophorin I , similar to
1809	14124976	kinesin family member C3
1810	14133213	Unknown
1811	14133215	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1812	14133217	Unknown
1813	14133235	Unknown
1814	14141157	heterogeneous nuclear ribonucleoprotein H3, isoform a
1815	14149607	chloride channel 7; ClC-7
1816	14149625	ND 20k
1817	14149649	siah binding protein 1; FBP interacting repressor; pyrimidine tract binding splicing factor; Ro ribonucleoprotein-binding protein 1
1818	14149677	lectomedin-3
1819	14149686	Unknown
1820	14149690	Unknown
1821	14149769	GAJ protein
1822	14149789	Unknown
1823	14149904	tumor endothelial marker 8, isoform 1 precursor; anthrax toxin receptor
1824	14149971	Unknown
1825	14150001	Unknown
1826	14150017	Unknown
1827	14150039	Unknown
1828	14150062	Unknown
1829	14150072	Unknown
1830	14150072	Unknown
1831	14150080	Unknown
1832	14150116	Unknown
1833	14150128	phosphodiesterase 5A
1834	14150134	Unknown
1835	14150155	Unknown
1836	14165260	Unknown
1837	14165270	mitochondrial ribosomal protein L13
1838	14192943	MEGF10 protein
1839	14194461	A kinase anchor protein 9
1840	14196457	protocadherin gamma subfamily A, 12, isoform 2 precursor; cadherin 21; fibroblast cadherin FIB3
1841	14196465	protocadherin gamma subfamily A, 3, isoform 2 precursor
1842	14198176	ND 51k
1843	14198272	Bcl-XL-binding protein v68 ,similar to
1844	14198303	Unknown
1845	14211536	neurexin 2; neurexin II
1846	14211570	conserved ERA-like GTPase
1847	14211720	desmuslin
1848	14211857	Unknown
1849	14211903	ubiquitin specific protease
1850	14211907	zinc finger protein 347; zinc finger 1111
1851	14211923	PKCI-1-related HIT protein

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1852	14211939	methylmalonyl-CoA epimerase
1853	14248761	cAMP-specific cyclic nucleotide phosphodiesterase
1854	14249144	RAB11B, member RAS oncogene family
1855	14249338	Unknown
1856	14249342	internexin neuronal intermediate filament protein, alpha; neurofilament 5 (66kD); neurofilament-66, tax-binding protein
1857	14249376	Unknown
1858	14249428	Unknown
1859	14249446	Unknown
1860	14249454	Unknown
1861	14249474	Unknown
1862	14249506	Unknown
1863	14249588	lactamase, beta
1864	14249596	Unknown
1865	14249620	Unknown
1866	14249967	staufenhomolog 2
1867	14250063	peroxiredoxin 3
1868	14250110	Unknown
1869	14250319	Unknown
1870	14250458	stromal cell derived factor 5 , similar to
1871	14250628	Unknown
1872	14250744	Unknown
1873	14251209	chloride intracellular channel 1
1874	14269578	metallothionein IV
1875	14277739	Erythrocyte Band-3 Protein,Crystal Structure Of The Cytoplasmic Domain Of Human
1876	14280050	Vps39/Vam6-like protein
1877	14285174	elongation factor G
1878	14286186	ZINC FINGER PROTEIN 185(P1-A) g
1879	14286294	Unknown
1880	14289323	LIP isoform of BLIP
1881	14318622	Unknown
1882	14329511	bA430M15.1 (novel protein (ortholog of rat four repeat ion channel))
1883	14329531	Unknown
1884	14336727	Unknown
1885	14336768	Unknown
1886	14336775	ND PDSW
1887	14349362	major histocompatibility complex, class I, F
1888	14424013	WNT-5B protein precursor
1889	14424776	Unknown
1890	14485049	T-cell receptor V delta 1

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1891	14488680	Phosphoglucose IsomeraseNEUROLEUKINAUTOCRINE MOTILITY FACTORMATURATION Factor
1892	14530763	citrate lyase, similar to
1893	14549163	Matrilin-2 precursor
1894	14571713	tonicity-responsive enhancer binding protein
1895	14575679	hemicentin
1896	14602477	DNA-BINDING PROTEIN A
1897	14602507	Unknown
1898	14602841	cysteine string protein 1
1899	14602856	Unknown
1900	14602907	Unknown
1901	14602977	Unknown
1902	14603084	putative DNA binding protein
1903	14603309	heat shock 60kD MITOCHONDRIAL
1904	14603403	stomatin-like 2
1905	14670360	zinc finger protein 278, long C isoform; POZ-AT hook-zinc finger protein
1906	14714447	sorting nexin 7
1907	14714514	DIHYDROLIPOAMIDE DEHYDROGENASE-BINDING PROTEIN OF PYRUVATE DEHYDROGENASE COMPLEX
1908	14714528	Unknown
1909	14715007	Unknown
1910	14719392	cofilin 2
1911	14720172	Unknown
1912	14720558	succinate dehydrogenase, flavoprotein subunit
1913	14721241	low density lipoprotein-related protein-associated protein 1
1914	14721350	testicular protein kinase 2
1915	14721365	hypothetical protein, estradiol-induced
1916	14721507	serine/threonine kinase 18
1917	14721966	Unknown
1918	14722003	cadherin 12, type 2
1919	14722193	3-hydroxybutyrate dehydrogenase
1920	14722283	Unknown
1921	14722554	Unknown
1922	14722589	mitochondrial ribosomal protein L22
1923	14722898	mitochondrial ribosomal protein S27
1924	14723145	acid phosphatase 1 isoform b
1925	14723407	Unknown
1926	14723451	mitochondrial ribosomal protein L20
1927	14723531	p25
1928	14724042	ASB-3 protein
1929	14724206	Unknown
1930	14724379	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1931	14724557	phosphatidylinositol glycan, class K
1932	14724575	Unknown
1933	14724751	phosphorylase, glycogen; brain
1934	14724805	Unknown
1935	14725181	lymphocyte antigen 75
1936	14725399	TNF-induced protein
1937	14725420	syntaxin 12
1938	14725545	RNA-binding protein regulatory subunit
1939	14725791	Unknown
1940	14725848	acyl-Coenzyme A dehydrogenase, C-4 to C-12 straight chain
1941	14726372	Unknown
1942	14726632	Unknown
1943	14726693	Unknown
1944	14726725	Unknown
1945	14726866	Unknown
1946	14727174	leucine-rich PPR-motif containing
1947	14727486	succinate dehydrogenase, subunit D
1948	14727827	Unknown
1949	14728081	excision repair cross-complementing rodent repair deficiency
1950	14728229	phosphoinositide-3-kinase, regulatory subunit 4, p150
1951	14728316	natural killer cell receptor 2B4
1952	14728439	Unknown
1953	14728817	Unknown
1954	14728839	Unknown
1955	14728858	sterol carrier protein 2
1956	14728945	DMRT-like family B with proline-rich C-terminal, 1
1957	14729172	elastin microfibril interface located protein
1958	14729475	BCL9
1959	14729487	mast cell carboxypeptidase A3 precursor
1960	14729783	dihydrolipoamide branched chain transacylase
1961	14730158	TATA element modulatory factor 1
1962	14730499	Unknown
1963	14730569	adenylate cyclase 3
1964	14730600	Unknown
1965	14730775	hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-Coenzyme A hydratase alpha
1966	14730782	kinesin heavy chain member 2
1967	14732014	Unknown
1968	14732481	calcium channel, voltage-dependent, alpha 1E subunit
1969	14732525	selective LIM binding factor, rat homolog
1970	14732721	adenomatosis polyposis coli
1971	14732789	mitofilin
1972	14732886	thyroid hormone receptor-associated protein, 150 kDa subunit

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
1973	14733183	adaptor-related protein complex 2, mu 1 subunit
1974	14733451	enkephalinase
1975	14733480	Unknown
1976	14733532	myofibrillogenesis regulator MR-1
1977	14733712	chondroitin sulfate proteoglycan 2
1978	14733904	serine/threonine kinase 16
1979	14734022	Unknown
1980	14734151	lymphoid enhancer binding factor-1
1981	14734205	Unknown
1982	14734243	Unknown
1983	14734441	Unknown
1984	14734746	DEAD/Hbox polypeptide 1
1985	14734864	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a-like 1
1986	14735060	mitochondrial isoleucine tRNA synthetase
1987	14735128	Ste-20 related kinase
1988	14735161	BCL6
1989	14735336	Unknown
1990	14735426	nuclear factor, interleukin 3 regulated
1991	14735687	Unknown
1992	14735741	Unknown
1993	14735899	cytochrome b5 reductase 1
1994	14736223	UCR 1
1995	14736227	Rho-associated, coiled-coil containing protein kinase 2
1996	14736267	protein disulfide isomerase-related protein
1997	14736397	Unknown
1998	14736560	Unknown
1999	14736612	Unknown
2000	14736678	lactotransferrin
2001	14736760	voltage-dependent anion channel 2
2002	14736866	DnaJhomolog, subfamily B, member 12
2003	14737445	sema domain, immunoglobulin domain (Ig), short basic domain,
2004	14737746	myeloid differentiation primary response gene
2005	14737907	Unknown
2006	14738004	Unknown
2007	14738099	Apobec-1 complementation factor; APOBEC-1 stimulating protein
2008	14738103	annexin IV
2009	14738306	putative , similar to
2010	14738689	Unknown
2011	14738950	Unknown
2012	14739002	Unknown
2013	14739106	Unknown
2014	14739392	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2015	14739472	potassium voltage-gated channel, shaker-related subfamily
2016	14739880	Unknown
2017	14740316	HEAT SHOCK 27 KDA PROTEIN (HSP 27) (STRESS-RESPONSIVE PROTEIN 27) (SRP27) (ESTROGEN-REGULATED 24 KDA PROTEIN) (28 KDA HEAT SHOCK PROTEIN) , similar to
2018	14740371	A kinase anchor protein 2
2019	14740403	thioredoxin
2020	14740476	TAF2 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 150 kD
2021	14740547	FUMARATE HYDRATASE, MITOCHONDRIAL PRECURSOR (FUMARASE)
2022	14740792	v-ral simian leukemia viral oncogene homolog A (ras related)
2023	14740886	Unknown
2024	14741177	Unknown
2025	14741234	Unknown
2026	14741376	Fas-activated serine/threonine kinase, isoform 2
2027	14741510	Unknown
2028	14741555	Unknown
2029	14741636	Unknown
2030	14741782	uncharacterized hematopoietic stem/progenitor cells protein MDS0
2031	14742266	RNA helicase
2032	14742273	Unknown
2033	14742317	Unknown
2034	14742600	vimentin
2035	14742688	diphthamide biosynthesis-like protein 2
2036	14742977	inter-alphainhibitor, H2 polypeptide
2037	14743031	Unknown
2038	14743873	TAR (HIV) RNA binding protein 1
2039	14744078	gamma filamin
2040	14744132	heat shock 70kD protein 5 (glucose-regulated protein, 78kD)
2041	14744234	nuclear receptor subfamily 6, group A, member 1, isoform 1
2042	14744290	Hermansky-Pudlak syndrome protein
2043	14744642	Unknown
2044	14744702	rat myomegalin , similar to
2045	14745217	lipocalin 2 (oncogene 24p3)
2046	14745424	spectrin, alpha, non-erythrocytic 1 (alpha-fodrin)
2047	14745489	wingless-type MMTV integration site family, member 3A
2048	14745808	guanine nucleotide binding proteinalpha 12
2049	14745853	Z-band alternatively spliced PDZ-motif
2050	14745861	Z-band alternatively spliced PDZ-motif
2051	14745865	Unknown
2052	14746475	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2053	14746487	ACYL-COA DEHYDROGENASE, VERY-LONG-CHAIN SPECIFIC+F36, similar to
2054	14746491	Unknown
2055	14746535	RAB7, member RAS oncogene family
2056	14746585	yeast adenylate cyclase, similar to
2057	14747216	carrier aralar
2058	14747249	CGI-135 protein
2059	14747260	serologically defined colon cancer antigen 1
2060	14747375	lysophospholipase I
2061	14747970	Unknown
2062	14748292	Unknown
2063	14748400	Unknown
2064	14748439	Unknown
2065	14748831	Unknown
2066	14748858	transformation/transcription domain-associated protein
2067	14749079	vacuolar protein sorting protein 18
2068	14749154	Unknown
2069	14749213	serine-threonine kinase/MAD3-like protein kinase
2070	14749294	GCN2 eIF2alpha kinase
2071	14749361	Unknown
2072	14749419	Unknown
2073	14749523	Unknown
2074	14749588	Unknown
2075	14749765	A kinase anchor protein 6
2076	14749776	Unknown
2077	14750136	Unknown
2078	14750148	Unknown
2079	14750186	LAMIN A/C (70 KDA LAMIN)
2080	14750222	Unknown
2081	14750259	Rho/Rac guanine nucleotide exchange factor 2
2082	14750405	pyruvate kinase, muscle (H. sapiens) , similar to
2083	14751203	Unknown
2084	14751493	N-acylsphingosine amidohydrolase
2085	14751551	Unknown
2086	14751705	Unknown
2087	14751808	purine nucleoside phosphorylase
2088	14751866	IGF-II mRNA-binding protein 3
2089	14752024	carrier aralar2
2090	14752229	dihydrolipoamide dehydrogenase
2091	14752236	Unknown
2092	14752239	laminin, beta 1 precursor
2093	14752249	spectrin, beta, erythrocytic (includes spherocytosis, clinical type I)

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2094	14752728	guanine nucleotide exchange factor Lbc or A-kinase anchoring protein
2095	14753117	Unknown
2096	14753239	kinectin 1
2097	14753384	A kinase (PRKA) anchor protein (gravin) 12
2098	14753693	adaptor-related protein complex 4, sigma 1 subunit , similar to
2099	14753915	Ras protein-specific guanine nucleotide-releasing factor 1
2100	14754222	farnesol receptor HRR-1
2101	14754627	Unknown
2102	14754848	Unknown
2103	14754867	Unknown
2104	14755192	Unknown
2105	14755316	zinc finger protein 91
2106	14755336	tumor rejection antigen1
2107	14755347	Unknown
2108	14755357	mitochondrial ribosomal protein L18
2109	14755436	superoxide dismutase 2, mitochondrial
2110	14755456	zinc finger protein 256
2111	14755952	lysophospholipase I, similar to
2112	14756295	Na,K-ATPase subunit alpha 3
2113	14756299	pot.ORF (1013 AA) , similar to
2114	14756626	DNA (cytosine-5)-methyltransferase
2115	14756630	mitochondrial ribosomal protein L4
2116	14756895	dUTP pyrophosphatase
2117	14756939	Unknown
2118	14756944	Unknown
2119	14757147	Unknown
2120	14757210	FSH primary responsehomolog 1
2121	14757677	phosphoglycerate kinase 1
2122	14757711	Unknown
2123	14758001	ND 24K NADH dehydrogenase (ubiquinone) flavoprotein 2 (24kD) (H. sapiens) , similar to
2124	14758520	ATPase, Cu++ transporting, beta polypeptide (Wilson disease)
2125	14759302	golgi autoantigen, golgin subfamily a, 3
2126	14759459	hook2 protein
2127	14759609	Unknown
2128	14759903	transcription factor
2129	14759981	Unknown
2130	14760649	inositol 1,4,5-triphosphate receptor, type 2
2131	14761208	glyceraldehyde 3-phosphate dehydrogenase like
2132	14761398	tubulin beta 5 , similar to
2133	14761496	programmed cell death 8 (apoptosis-inducing factor)
2134	14761689	calcium channel, voltage-dependent, beta 3 subunit

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2135	14762250	protein tyrosine phosphatase, receptor type, B
2136	14762650	Unknown
2137	14762696	granzyme M precursor
2138	14763105	Unknown
2139	14763304	src homology 2 domain-containing transforming protein D, similar to
2140	14763427	death-associated protein kinase 3, ZIP-kinase
2141	14763491	NY-REN-58 antigen
2142	14763709	Unknown
2143	14763948	FERM, RhoGEF, and pleckstrin domain protein 1; chondrocyte-derived ezrin-like protein , similar to
2144	14764159	acetyl-Coenzyme A acyltransferase 2 (mitochondrial 3-oxoacyl-CoenzymeA thiolase)
2145	14764202	hydroxyacyl-Coenzyme A dehydrogenase, type II
2146	14764412	D-amino-acid oxidase
2147	14764458	male-specific lethal-3 (Drosophila)-like 1
2148	14764705	Unknown
2149	14764874	Unknown
2150	14764936	G protein-coupled receptor 19
2151	14765579	Unknown
2152	14765581	peroxiredoxin 5
2153	14765684	kinesin family member 4
2154	14766197	Unknown
2155	14766265	Unknown
2156	14766346	glutathione S-transferase P1-1
2157	14766373	regulatory factor X, 4
2158	14766393	transmembrane protein (63kD), endoplasmic reticulum/Golgi
2159	14766635	prohibitin, B-cell associated protein
2160	14766937	DRIM protein or Key-1A6 protein
2161	14767036	Unknown
2162	14767224	protein kinase C and casein kinase substrate
2163	14767305	protein C, cardiac
2164	14767738	CALCIUM ATPASE 2(SERCA2)
2165	14767795	Unknown
2166	14768227	purinergic receptor P2X, ligand-gated ion channel, 7
2167	14768743	thioredoxin peroxidase
2168	14769051	ND B14.5a
2169	14769064	Unknown
2170	14769085	Unknown
2171	14769089	Unknown
2172	14769268	GalNAc alpha-2, 6-sialyltransferase I, long form
2173	14769776	peripheral benzodiazepine receptor-associated protein 1
2174	14770042	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2175	14770070	Unknown
2176	14770170	Unknown
2177	14770383	Unknown
2178	14770569	Unknown
2179	14770608	small fragment nuclease
2180	14770670	Unknown
2181	14770915	Unknown
2182	14770940	angiotensin I converting enzyme
2183	14770968	Unknown
2184	14771355	beta-2-glycoprotein I precursor
2185	14771369	brain-immunoglobulin-like molecule with tyrosine-based activation motifs
2186	14771396	isocitrate dehydrogenase 3 beta (NAD+)
2187	14771416	murine retrovirus integration site 1 homolog
2188	14771689	myosin, heavy polypeptide 1, skeletal muscle, adult
2189	14772046	Unknown
2190	14772333	phosphorylase, glycogen; brain (H. sapiens) , similar to
2191	14772527	Unknown
2192	14772555	Unknown
2193	14772672	calpain 5
2194	14772954	copine I
2195	14773504	tyrosine kinase, non-receptor, 1
2196	14773592	AHNAK nucleoprotein (desmoyokin)
2197	14773948	Unknown
2198	14774045	Unknown
2199	14774139	ATPase g
2200	14774236	Unknown
2201	14774282	apolipoprotein A-I precursor
2202	14774359	ionotropic ATP receptor P2X5b
2203	14774503	phospholipase D2
2204	14774525	carrier oxoglutarate
2205	14774778	Unknown
2206	14774780	karyopherin (importin) beta 1
2207	14774844	succinate dehydrogenase, subunit C
2208	14775218	Unknown
2209	14775320	Unknown
2210	14775363	baculoviral IAP repeat-containing protein 5
2211	14775444	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 5, similar to
2212	14775476	endocytic receptor (macrophage mannose receptor family)
2213	14775546	malonyl-CoA decarboxylase
2214	14775827	ubiquinol-cytochrome c reductase core protein II
2215	14775827	UCR 2

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2216	14776296	Unknown
2217	14776472	nuclear receptor co-repressor 1
2218	14776681	Unknown
2219	14776736	Unknown
2220	14776778	ATP-binding cassette, sub-family A member 3
2221	14776800	cat eye syndrome chromosome region, candidate 5, isoform 1
2222	14776960	Unknown
2223	14776980	carrier citrate transporter
2224	14777215	protein disulfide isomerase, pancreatic; protein disulfide isomerase , similar to
2225	14777313	ND 13k-B
2226	14777483	general transcription factor IIIC, polypeptide 1 (alpha subunit, 220kD)
2227	14777522	Unknown
2228	14777630	AT-binding transcription factor 1
2229	14777716	Unknown
2230	14777813	Unknown
2231	14777901	Unknown
2232	14778035	Unknown
2233	14778104	adaptor-related protein complex 1, beta 1 subunit
2234	14778235	Unknown
2235	14778381	eIF4E-transporter
2236	14778431	ret finger protein-like 2
2237	14778654	THIOSULFATE SULFURTRANSFERASE (RHODANESE)
2238	14779326	Unknown
2239	14779686	Unknown
2240	14779867	N-acetylglucosamine-1-phosphodiester alpha-N-acetylglucosaminida
2241	14779881	periplakin
2242	14779964	Unknown
2243	14780055	protease, serine, 7
2244	14780117	Unknown
2245	14780193	synaptojanin 1
2246	14780272	intersectin 1 (SH3 domain protein)
2247	14780668	ES1 protein /KNP-I protein ?? (ThiJ/Pfpl family motif)
2248	14780705	phosphofructokinase, liver
2249	14780857	Unknown
2250	14781094	huntingtin
2251	14781125	quinoid dihydropteridine reductase (H. sapiens) , similar to
2252	14781245	fatty-acid-Coenzyme A ligase, long-chain 6
2253	14781533	Unknown
2254	14781826	receptor (TNFRSF)-interacting serine-threonine kinase 1
2255	14781890	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2256	14781979	Unknown
2257	14781989	putative transcription factor/GTF2I repeat domain-containing 1, isoform 2
2258	14782063	malate dehydrogenase 2, NAD (mitochondrial)
2259	14782332	HLA-B associated transcript-3 , similar to
2260	14782751	Unknown
2261	14782921	protein kinase C and casein kinase substrate in neurons 1
2262	14782973	tubby like protein 1
2263	14783011	p38 mitogen-activated protein kinase
2264	14783112	Unknown
2265	14783333	supervillin, isoform 1
2266	14783455	Unknown
2267	14783504	Unknown
2268	14783675	small GTP binding protein RAB6 isoform
2269	14783738	inositol polyphosphate phosphatase-like 1
2270	14784011	Unknown
2271	14784064	mitogen-activated protein kinase kinase kinase 11
2272	14784122	atrophin-1
2273	14784162	Ubiquitin isopeptidase T
2274	14784612	Unknown
2275	14784913	EH-domain containing 4
2276	14785008	Unknown
2277	14785181	microfibrillar-associated protein 1
2278	14785356	Unknown
2279	14785405	polo (Drosophia)-like kinase
2280	14785865	Unknown
2281	14785919	copper containing amine oxidase 3 precursor; amine oxidase (copper-containing);copper amine oxidase precursor ;vascular adhesion protein 1; vascular adhesion protein 1 , similar to
2282	14786231	Unknown
2283	14786366	PAR-6 beta
2284	14786394	cytochrome P450, subfamily XXIV precursor
2285	14786884	Unknown
2286	14787181	CUB and sushi multiple domains protein 1 short form
2287	14790190	SMART/HDAC1 associated repressor protein
2288	15012003	Unknown
2289	15012048	HERV-H LTR-associating 3, similar to
2290	15020655	ATP/GTP-binding protein
2291	15026974	obscurin
2292	15029619	fracture callus 1homolog
2293	15029922	Unknown
2294	15030240	ATPase alpha, H+ transporting, mitochondrial F1 complex, alpha subunit, isoform 1, cardiac muscle , similar to

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2295	15041811	Hermansky-Pudlak syndrome type-3 protein
2296	15076827	Pcph proto-oncogene protein
2297	15079348	angiotensinogen proteinase inhibitor,
2298	15079392	replication control protein 1
2299	15079408	Unknown
2300	15079735	Unknown
2301	15080291	dipeptidyl peptidase 7+F206, similar to
2302	15080429	Unknown
2303	15080454	Unknown
2304	15080499	serineproteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1, similar to
2305	15126735	heat shock 27kD protein 1 , similar to
2306	15147248	putative breast epithelial stromal interaction protein
2307	15147337	progestin induced protein; ubiquitin-protein ligase [Homo sa
2308	15149476	arginyl-tRNA synthetase
2309	15150811	mitochondrial ribosomal protein S36
2310	15208648	central cannabinoid receptor, isoform b; CB1 receptor; brain cannabinoid receptor 1
2311	15213479	putative DNA polymerase delta p38 subunit
2312	15213542	NSD1
2313	15214423	Unknown
2314	15214486	Unknown
2315	15214706	Unknown
2316	15215308	dystroglycan 1, similar to
2317	15227456	ch-TOG protein from Homo sapiens [Arabidopsis tha
2318	15277229	Homologue to Drosophila photoreceptor protein calphotin
2319	15277415	scavenger receptor cysteine-rich type 1 protein M160 precursor
2320	15277514	Unknown
2321	15278188	Unknown
2322	15281150	unkempt (Drosophila)-like
2323	15281837	PX domain-containing protein kinase
2324	15294558	RAS-RELATED PROTEIN RAB-5A
2325	15294560	RAB5A, member RAS oncogene family
2326	15294667	bassoon (presynaptic cytomatrix protein)
2327	15294817	GalNAc-4-sulfotransferase 2 (H. sapiens) , similar to
2328	15295270	MADhomolog 5
2329	15295351	VDAC-1
2330	15295412	Unknown
2331	15295574	laminin receptor 1
2332	15295842	Unknown
2333	15296104	optic atrophy 1
2334	15296351	splicing factor 3b, subunit 1, 155kD
2335	15296762	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2336	15296824	lipin 1
2337	15297926	transforming growth factor, alpha
2338	15298022	mitochondrial ribosomal protein L53
2339	15299136	Unknown
2340	15299287	Unknown
2341	15299581	Unknown
2342	15299784	glutamate receptor, metabotropic 1
2343	15299942	Unknown
2344	15300149	modulator of transcription factor GATA-4 in cardiomyocytes
2345	15301488	SERINE/THREONINE PROTEIN KINASE 24(MST-3)
2346	15302083	CD2-associated protein
2347	15302719	Unknown
2348	15302936	citrate synthase precursor
2349	15303880	Glutamate receptor interacting protein
2350	15304843	Unknown
2351	15304935	destrin (actin depolymerizing factor)
2352	15305404	Unknown
2353	15305472	troponin I, cardiac
2354	15305838	RelA-associated inhibitor
2355	15306072	transcriptional repressor NAC1
2356	15306753	Unknown
2357	15307117	rho guanine nucleotide exchange factor 12
2358	15307634	ND 23k
2359	15314651	oxygen regulated protein
2360	15318843	aconitase 2, mitochondrial
2361	15318933	cytochrome b5 reductase
2362	15321298	Unknown
2363	15321380	v-erb-a avian erythroblastic leukemia viral oncogene homolog-like 4
2364	15321446	Unknown
2365	15341707	Unknown
2366	15375094	RSK-like protein
2367	15451842	ADAM-TS disintegrin and metalloproteinase domain 19, isoform 1 preproprotein; meltrin beta; metalloprotease-disintegrin meltrin beta
2368	15451854	midline 1, isoform beta; midline-1; zinc finger X and Y
2369	15451916	bone morphogenetic protein receptor, type II, isoform 1 precursor; type II activin receptor-like kinase; serine/threonine kinase
2370	15451923	serologically defined colon cancer antigen 33
2371	15529996	son of sevenless homolog 1 (Drosophila); son of sevenless (Drosophila) homolog 1
2372	15530243	villin 2 (ezrin) , similar to
2373	15530305	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2374	15553127	hexokinase 2; hexokinase-2, muscle
2375	15553137	H2A-Bbd
2376	15559225	Unknown
2377	15559303	Unknown
2378	15559516	Unknown
2379	15559753	Unknown
2380	15620821	Unknown
2381	15620841	Unknown
2382	15620853	Unknown
2383	15620867	Unknown
2384	15620879	Unknown
2385	15620927	Unknown
2386	15620933	Unknown
2387	15680004	H2B histone family, member Q , similar to
2388	15680171	semaF cytoplasmic domain associated protein 3
2389	15718530	POM121 membrane glycoprotein (rat homolog)-like 2
2390	15778991	Unknown
2391	15779080	Unknown
2392	15779126	guanine nucleotide binding protein (G protein), a
2393	15779156	Unknown
2394	15795410	Unknown
2395	15808373	erythroid membrane-associated protein
2396	15808607	ATPase f F0
2397	15826629	Peroxiredoxin 5
2398	15928608	solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 5 , similar to
2399	15928907	Unknown
2400	15929030	Unknown
2401	15929352	mitochondrial ribosomal protein L1
2402	15929856	Unknown
2403	15929892	Unknown
2404	15988268	Myb-Domain Of Human Rap1
2405	15988350	Lysozyme
2406	15990494	Unknown
2407	15991827	hexokinase 1, isoform HKI-R; brain form
2408	15991829	hexokinase 1, isoform HKI-ta/tb; brain form hexokinase
2409	15991859	Unknown
2410	16033591	SH2 domain-containing phosphatase anchor protein 2b
2411	16041807	Unknown
2412	16156815	Sec23-interacting protein p125
2413	16156952	Unknown
2414	16157047	succinate dehydrogenase complex, subunit A, flavoprotein precursor

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2415	16157111	progesterone membrane binding protein
2416	16157253	uridine 5 monophosphate hydrolase 1; pyrimidine 5-nucleotidase, similar to
2417	16157453	Unknown
2418	16157682	IDN3 protein
2419	16158005	RNA-binding protein regulatory subunit
2420	16158038	putative , similar to
2421	16158324	heat shock 70kD protein (Mortalin-2)
2422	16158747	CLIP-associating protein 2
2423	16159170	Unknown
2424	16159302	Unknown
2425	16159416	Unknown
2426	16159569	Unknown
2427	16159594	carnitine palmitoyltransferase II
2428	16159701	ribosomal protein S7 (H. sapiens) , similar to
2429	16159788	S100 calcium-binding protein A6
2430	16159874	Unknown
2431	16160276	spectrin, beta, non-erythrocytic 1 (H. sapiens) , similar to
2432	16160441	putative , similar to
2433	16160793	glycosyltransferase AD-017
2434	16160823	phosphatidylinositol-4-phosphate 5-kinase, type I, beta
2435	16160929	retinoblastoma-binding protein 5
2436	16161569	ryanodine receptor 2
2437	16161583	endoplasmic reticulum oxidoreductin 1-Lbeta
2438	16161627	Rho guanine nucleotide exchange factor 10
2439	16161681	Unknown
2440	16161727	stromal cell derived factor receptor 1 isoform a
2441	16162032	PEPTIDYL-PROLYL CIS-TRANS ISOMERASE B PRECURSOR (PPIASE) (ROTAMASE) (CYCLOPHILIN B)
2442	16163057	Unknown
2443	16163065	RIKEN cDNA 2410008H17 gene , similar to
2444	16163124	TTF-I interacting peptide 20
2445	16163817	Bcl 1
2446	16164710	Unknown
2447	16164895	rabaptin-5
2448	16164980	Unknown
2449	16165190	Unknown
2450	16165554	Unknown
2451	16165872	accessory proteins BAP31/BAP29 (H. sapiens) , similar to
2452	16166325	Unknown
2453	16166513	pericentrin B
2454	16168619	Unknown
2455	16171486	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2456	16171987	monoamine oxidase A
2457	16172349	triadin
2458	16174655	Unknown
2459	16175846	atrophin-1 interacting protein 1; activin receptor interacting protein
2460	16176937	excision repair protein 1
2461	16177368	putative , similar to
2462	16177559	MLL2 protein
2463	16178062	Unknown
2464	16178117	Unknown
2465	16178214	GTP-rho binding protein 1, similar to
2466	16181084	G protein-coupled receptor 51
2467	16192638	isocitrate dehydrogenase 2 (NADP+), mitochondrial
2468	16196598	cox 6a
2469	16198361	Unknown
2470	16198481	Unknown
2471	16306537	cadherin 20, type 2 preproprotein
2472	16306954	Unknown
2473	16306978	annexin A2
2474	16307164	CGI-90 protein
2475	16307227	Unknown
2476	16307270	Unknown
2477	16307468	Unknown
2478	16307475	neuroepithelial cell transforming gene 1
2479	16359102	Unknown
2480	16359195	Unknown
2481	16416451	tRNA-nucleotidyltransferase
2482	16418373	Unknown
2483	16418423	guanylate binding protein 4
2484	16507813	tumor necrosis factor receptor superfamily, member 21, similar to
2485	16549125	Unknown
2486	16549199	Unknown
2487	16549271	Unknown
2488	16549294	Unknown
2489	16549620	Unknown
2490	16549880	Unknown
2491	16549918	Unknown
2492	16550394	Unknown
2493	16550518	Unknown
2494	16550576	Unknown
2495	16550810	Unknown
2496	16550845	Unknown
2497	16551173	Unknown
2498	16551429	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2499	16551580	Unknown
2500	16551610	Unknown
2501	16551739	myosin light chain kinase
2502	16551769	Unknown
2503	16551917	Unknown
2504	16551953	Unknown
2505	16551957	Unknown
2506	16552104	Unknown
2507	16552271	Unknown
2508	16552547	Unknown
2509	16552885	Unknown
2510	16552927	Unknown
2511	16552957	Unknown
2512	16552988	Unknown
2513	16553031	Unknown
2514	16553078	Unknown
2515	16553235	Unknown
2516	16553285	Unknown
2517	16553362	Unknown
2518	16554014	Unknown
2519	16554275	Unknown
2520	16554604	mitochondrial ribosomal protein S23
2521	16554607	mitochondrial ribosomal protein S10; NB4 apoptosis/differentiation related protein; mitochondrial 28S ribosomal protein S10
2522	16741033	protease 26S subunit, ATPase 1
2523	16753264	Unknown
2524	16876860	Unknown
2525	16877071	ATPase gamma F1
2526	16877127	synaptophysin-like protein, similar to
2527	16877285	duodenal cytochrome b , similar to
2528	16877328	Unknown
2529	16877328	Unknown
2530	16877459	Unknown
2531	16877964	isovaleryl Coenzyme A dehydrogenase
2532	16878101	Unknown
2533	16924265	Unknown
2534	16924269	Unknown
2535	16950603	mitochondrial ribosomal protein S35; mitochondrial 28S ribosomal protein S28
2536	16950609	mitochondrial ribosomal protein S27; mitochondrial 28S ribosomal protein S27
2537	16974753	sodium-potassium-chloride cotransporter
2538	17016315	olfactory receptor-like protein JCG4

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2539	17028367	gelsolin (amyloidosis, Finnish type) , similar to
2540	17028379	Unknown
2541	17375734	Cyclin G-associated kinase
2542	17378599	Gamma-interferon-inducible protein Ifi-16 (Interferon-inducible myeloid differentiation transcriptional activator) (IFI 16)
2543	17380287	Mitochondrial 39S ribosomal protein L56 (MRP-L56) (Serine beta lactamase-like protein LACTB)
2544	17380426	Mannosyl-oligosaccharide 1,2-alpha-mannosidase IA (Processing alpha-1,2-mannosidase IA) (Alpha-1,2-mannosidase IA) (Mannosidase alpha class 1A member 1) (Man(9)-alpha-mannosidase) (Man9-mannosidase)
2545	17389971	Unknown
2546	17402865	thiosulfate sulfurtransferase (rhodanese)
2547	17432231	MSTP022
2548	17434094	putative , similar to
2549	17434314	Unknown
2550	17434411	Unknown
2551	17434458	Unknown
2552	17434554	Unknown
2553	17434671	Unknown
2554	17435264	INNER EAR-SPECIFIC COLLAGEN PRECURSOR (SACCULAR COLLAGEN) , similar to
2555	17435299	Unknown
2556	17435748	phosphorylase, glycogen; brain
2557	17436258	ND 13K-B NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5; hypothetical protein FLJ12147; Complex I-13KD-B; ubiquinone reductase; type I dehydrogenase , similar to
2558	17436498	Unknown
2559	17436513	VDAC-1 VOLTAGE-DEPENDENT ANION-SELECTIVE CHANNEL PROTEIN 1 (VDAC-1) (RVDAC1) (OUTER MITOCHONDRIAL MEMBRANE PROTEIN PORIN 1) , similar to
2560	17436561	Unknown
2561	17436979	Unknown
2562	17437312	Unknown
2563	17438284	Unknown
2564	17439551	REGULATOR OF G-PROTEIN SIGNALING 12 (RGS12) , similar to
2565	17440287	anaplastic lymphoma kinase Ki-1 , similar to
2566	17442134	one twenty two protein; hypothetical protein FLJ12479 , similar to
2567	17442500	Molybdenum cofactor synthesis protein cinnamon , similar to
2568	17442568	Unknown
2569	17443010	hematological and neurological expressed sequence 1 , similar to
2570	17443439	Unknown
2571	17443833	glyceraldehyde-3-phosphate dehydrogenase , similar to

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2572	17444067	RIKEN cDNA 0610011N22 , similar to
2573	17444600	Unknown
2574	17444969	solute carrier family 4, anion exchanger, member 3
2575	17445877	xylulokinase homolog (H. influenzae)
2576	17446038	Unknown
2577	17446807	plastin 1
2578	17447126	Unknown
2579	17447383	Unknown
2580	17447877	Unknown
2581	17450039	Unknown
2582	17450491	factor V , similar to
2583	17451676	putative , similar to
2584	17451748	Unknown
2585	17451801	Unknown
2586	17452377	Unknown
2587	17454350	putative protein , similar to
2588	17454582	phosphoglycerate mutase 1 (brain); Phosphoglycerate mutase A, nonmuscle form , similar to
2589	17455099	putative , similar to
2590	17455439	heat shock 60kD protein 1 (chaperonin) (H. sapiens) , similar to
2591	17455445	Mitochondrial Complex I protein, now 21754001
2592	17455927	Unknown
2593	17456092	Unknown
2594	17456384	non-specific cross reacting antigen , similar to
2595	17457389	Unknown
2596	17458483	Unknown
2597	17458911	Unknown
2598	17459115	Melanoma-associated antigen 11 (MAGE-11 antigen) , similar to
2599	17459319	putative , similar to
2600	17459408	small Rho-like GTPase RhoA , similar to
2601	17459479	Unknown
2602	17459746	VOLTAGE-DEPENDENT ANION-SELECTIVE CHANNEL PROTEIN 2 (OUTER MITOCHONDRIAL MEMBRANE PROTEIN PORIN 2) , similar to
2603	17460020	Unknown
2604	17460330	Unknown
2605	17460767	Unknown
2606	17460836	testis expressed sequence 13A , similar to
2607	17461025	Unknown
2608	17461670	RIKEN cDNA 9430083G14 , similar to
2609	17462761	Unknown
2610	17463437	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2611	17464527	match: multiple proteins; match: Q08151 P28185 Q01111 Q43554; match: Q08150 Q40195 P20340 Q39222; match: Q40368 P36412 P40393 Q40723; match: CE01798 Q38923 Q40191 Q41022; match: Q39433 Q40177 Q40218 Q08146; match: P10949 P11023 Q, similar to
2612	17464573	Unknown
2613	17464724	eukaryotic translation elongation factor 1 alpha 1 , similar to
2614	17464807	phosphoglycerate mutase 2 (muscle)
2615	17464864	Unknown
2616	17465135	v-raf murine sarcoma viral oncogene homolog B1
2617	17465213	Unknown
2618	17465562	Unknown
2619	17466365	Unknown
2620	17466818	Unknown
2621	17468096	prohibitin , similar to
2622	17468798	Unknown
2623	17469624	Unknown
2624	17470256	Unknown
2625	17470269	chromosome 15 open reading frame 2 , similar to
2626	17470290	Unknown
2627	17471316	Unknown
2628	17471893	Unknown
2629	17472555	Unknown
2630	17472883	ND 51K NADH dehydrogenase (ubiquinone) flavoprotein 1 (51kD)
2631	17474293	midline 1; Finger on X and Y (in rat only on X) , similar to
2632	17474785	VDAC-1 voltage-dependent anion channel 1 , similar to
2633	17475184	Y39B6A.pp.p , similar to
2634	17476245	Unknown
2635	17476469	Unknown
2636	17476471	Unknown
2637	17478738	Unknown
2638	17481443	procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), beta polypeptide (protein disulfide isomerase; thyroid hormone binding protein p55)
2639	17481778	Unknown
2640	17482059	Unknown
2641	17482696	Kruppel-type zinc finger (C2H2) , similar to
2642	17482910	Unknown
2643	17482953	putative methyl-binding domain protein MBD105 , similar to
2644	17483121	rhophilin-like protein (H. sapiens) , similar to
2645	17483187	Unknown
2646	17483399	RAB11B, member RAS oncogene family
2647	17483482	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2648	17484820	acetyl-Coenzyme A synthetase 2 (AMP forming)-like
2649	17484835	Unknown
2650	17485036	Unknown
2651	17485099	Unknown
2652	17485128	Unknown
2653	17485337	Unknown
2654	17485700	Unknown
2655	17485787	Mitochondrial Acyl-CoA Thioesterase
2656	17486071	DKFZP434O047 protein , similar to
2657	17486087	Unknown
2658	17486456	Unknown
2659	17486463	Unknown
2660	17486622	Unknown
2661	17486915	Unknown
2662	17487175	dentin phosphoryn , similar to
2663	17487390	Unknown
2664	17487672	Unknown
2665	17487733	F40G9.9.p , similar to
2666	17487809	glyceraldehyde-3-phosphate dehydrogenase , similar to
2667	17487981	F4N2.10 , similar to
2668	17488153	Unknown
2669	17489631	Unknown
2670	17491107	Unknown
2671	17511874	Unknown
2672	17511976	Unknown
2673	17512080	WAS protein family, member 1
2674	17512147	Unknown
2675	17736731	mixed lineage kinase 4beta
2676	17834080	haymaker protein
2677	17865554	mitochondrial ribosomal protein L9, 60S mitochondrial precursor (L9mt)
2678	17939563	Unknown
2679	17943068	Tcf-4 BETA-Catenin Complex
2680	17943407	Auh Protein, An Rna-Binding Homologue Of Enoyl-Coa Hydratase
2681	17981863	ND 5
2682	17985539	ND 4
2683	18044194	Unknown
2684	18087815	Unknown
2685	18088572	RIKEN cDNA 4930553C05 gene , similar to
2686	18147097	CG1800 gene product [Drosophila melanogaster] homolog
2687	18157651	bullous pemphigoid antigen 1 eA
2688	18158416	chromosome 20 open reading frame 188 protein; likely ortholog of mouse transient receptor protein 4, associated protein

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2689	18201886	chromosome 20 open reading frame 175
2690	18201913	winged-helix nude
2691	18204214	Unknown
2692	18204272	Unknown
2693	18252315	propionyl-CoA carboxylase alpha subunit
2694	18252778	ankyrin repeat-containing protein ASB-2
2695	18490293	ephrin B3 , similar to
2696	18490363	calsequestrin 2 (cardiac muscle)
2697	18490389	Unknown
2698	18490639	Unknown
2699	18543654	Unknown
2700	18543672	Unknown
2701	18544062	Unknown
2702	18544103	transcription factor Dp-1 , similar to
2703	18544502	Unknown
2704	18545149	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily f, member 1 (H. sapiens) , similar to
2705	18545197	Unknown
2706	18545286	Unknown
2707	18545525	Unknown
2708	18545711	trithorax-related , similar to
2709	18545867	forkhead box D2
2710	18546369	Unknown
2711	18546495	N-acetylglucosaminyltransferase VI , similar to
2712	18547145	Unknown
2713	18547604	Unknown
2714	18547655	Unknown
2715	18547774	PAPIN , similar to
2716	18547995	Unknown
2717	18548319	Unknown
2718	18548686	Unknown
2719	18548841	Unknown
2720	18549011	Unknown
2721	18549603	Unknown
2722	18549721	spectrin, alpha, erythrocytic 1 (elliptocytosis 2)
2723	18549759	Unknown
2724	18550245	Unknown
2725	18550248	dysferlin
2726	18550356	Unknown
2727	18550688	LWamide neuropeptide precursor protein , similar to
2728	18551342	laminin receptor 1; Laminin receptor-1 (67kD); 67kD, ribosomal protein SA , similar to
2729	18551404	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2730	18551428	Unknown
2731	18551530	Unknown
2732	18551750	Unknown
2733	18552428	down-regulated by Ctnnb1, a , similar to
2734	18552574	heat shock 70kD protein 9B (mortalin-2) (H. sapiens) , similar to
2735	18552843	Unknown
2736	18553054	Unknown
2737	18553524	Unknown
2738	18553646	Unknown
2739	18553709	RIKEN cDNA 1810055D05 gene , similar to
2740	18553922	succinate dehydrogenase complex, subunit A, flavoprotein (Fp) (H. sapiens) , similar to
2741	18554092	Unknown
2742	18554792	Unknown
2743	18554892	protein phosphatase 4 regulatory subunit 2 (H. sapiens) , similar to
2744	18555498	Unknown
2745	18555697	SALL1 (sal (Drosophila)-like , similar to
2746	18555923	Unknown
2747	18556527	protein tyrosine phosphatase, receptor type, G
2748	18557013	Unknown
2749	18557341	Unknown
2750	18557515	ring finger protein 23; RING-B box-coiled coil-B30.2 , similar to
2751	18557535	Unknown
2752	18557606	Unknown
2753	18557689	Unknown
2754	18558040	Unknown
2755	18558112	C-terminal binding protein 1 (H. sapiens) , similar to
2756	18558130	cyclin G associated kinase (H. sapiens) , similar to
2757	18558177	Unknown
2758	18558348	Unknown
2759	18558362	Unknown
2760	18558762	Unknown
2761	18559050	Unknown
2762	18559054	Unknown
2763	18559169	GrpE-like protein cochaperone
2764	18559889	Unknown
2765	18559896	Unknown
2766	18559969	Unknown
2767	18559997	Unknown
2768	18560088	Unknown
2769	18560396	Unknown
2770	18560536	Unknown
2771	18560871	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2772	18560910	SGC32445 protein
2773	18561153	Unknown
2774	18561225	Unknown
2775	18561342	Unknown
2776	18561850	Unknown
2777	18562164	Unknown
2778	18562264	Unknown
2779	18562403	gag , similar to
2780	18562447	Unknown
2781	18562613	Unknown
2782	18562676	Unknown
2783	18562743	Unknown
2784	18562778	Unknown
2785	18562814	Unknown
2786	18562826	Unknown
2787	18563024	Unknown
2788	18563079	Unknown
2789	18563446	Unknown
2790	18564249	Unknown
2791	18565200	Unknown
2792	18565553	Unknown
2793	18565735	Unknown
2794	18565792	Unknown
2795	18565965	Unknown
2796	18566008	Unknown
2797	18566051	Unknown
2798	18566469	CDC14 cell division cycle 14 homolog B (S. cerevisiae) (H. sapiens) , similar to
2799	18566582	Unknown
2800	18567546	Unknown
2801	18568015	Unknown
2802	18568092	Unknown
2803	18568100	Unknown
2804	18568732	Unknown
2805	18568834	Unknown
2806	18568892	T-COMPLEX PROTEIN 1, GAMMA SUBUNIT (TCP-1-GAMMA) (CCT-GAMMA) , similar to
2807	18568988	Unknown
2808	18569016	Unknown
2809	18569389	Unknown
2810	18569391	Unknown
2811	18569544	Unknown
2812	18569728	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2813	18569926	Unknown
2814	18570016	Unknown
2815	18570037	Unknown
2816	18571373	Unknown
2817	18571864	Unknown
2818	18572080	tubulin, beta polypeptide 4, member Q (H. sapiens) , similar to
2819	18572219	Unknown
2820	18572532	Unknown
2821	18572576	DKFZP434J193 protein (H. sapiens) , similar to
2822	18572752	Unknown
2823	18573432	Unknown
2824	18573604	Unknown
2825	18573884	Sec24-related protein C
2826	18574091	(H. sapiens) , similar to
2827	18574564	Unknown
2828	18574897	cathepsin L , similar to
2829	18575014	Unknown
2830	18575020	Unknown
2831	18575034	Unknown
2832	18575353	Unknown
2833	18575792	Unknown
2834	18575881	solute carrier family 9 (sodium/hydrogen exchanger), isoform 3 , similar to
2835	18575937	Unknown
2836	18576372	Unknown
2837	18576435	glycoprotein beta-Gal 3'-sulfotransferase (H. sapiens) , similar to
2838	18576618	Unknown
2839	18576708	Unknown
2840	18576758	Unknown
2841	18576861	Unknown
2842	18577160	Unknown
2843	18577199	suppression of tumorigenicity 5
2844	18577427	Unknown
2845	18577553	Unknown
2846	18577877	glutamate receptor, metabotropic 5 (H. sapiens) , similar to
2847	18578024	Unknown
2848	18578981	voltage gated potassium channel Kv3.2b , similar to
2849	18579037	glyceraldehyde-3-phosphate dehydrogenase , similar to
2850	18579791	Unknown
2851	18580015	Unknown
2852	18580073	Unknown
2853	18580116	solute carrier family 4, sodium bicarbonate cotransporter, member 8 (H. sapiens) , similar to

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2854	18580149	Unknown
2855	18580193	Unknown
2856	18580223	Unknown
2857	18580396	Unknown
2858	18580585	Unknown
2859	18580633	phosphoinositide-3-kinase, class 2, gamma polypeptide
2860	18581005	Unknown
2861	18581215	Unknown
2862	18581598	Unknown
2863	18581873	Unknown
2864	18582200	Unknown
2865	18582274	Unknown
2866	18582343	Unknown
2867	18582592	Unknown
2868	18582682	CG9109 gene product , similar to
2869	18582865	Unknown
2870	18583213	Unknown
2871	18583325	Unknown
2872	18583345	Unknown
2873	18583383	Unknown
2874	18583657	Unknown
2875	18583725	multidomain presynaptic cytomatrix protein Piccolo , similar to
2876	18583727	Unknown
2877	18584065	Unknown
2878	18584949	Unknown
2879	18585335	Unknown
2880	18585686	Unknown
2881	18586054	Unknown
2882	18586298	Unknown
2883	18586333	splicing factor 3b, subunit 3, 130kD
2884	18586459	putative , similar to
2885	18586610	Unknown
2886	18587004	Unknown
2887	18587044	Unknown
2888	18587067	Unknown
2889	18587111	Unknown
2890	18587387	Unknown
2891	18587810	arachidonate 12-lipoxygenase, 12R type (H. sapiens) , similar to
2892	18588235	Unknown
2893	18588450	Unknown
2894	18588517	Unknown
2895	18589035	Unknown
2896	18589065	WW domain binding protein-2 , similar to

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2897	18589260	Unknown
2898	18589408	Unknown
2899	18589876	Unknown
2900	18590023	Unknown
2901	18590390	RNI-like protein , similar to
2902	18590417	Unknown
2903	18590816	Unknown
2904	18591174	Unknown
2905	18591441	ND B14.5a NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 7 (14.5kD, B14.5a)
2906	18591813	Unknown
2907	18592023	Unknown
2908	18592069	Unknown
2909	18592852	Unknown
2910	18593545	Unknown
2911	18593908	Unknown
2912	18593939	secretory protein 45 kDa , similar to
2913	18594017	Unknown
2914	18594189	Unknown
2915	18594359	Unknown
2916	18594592	Unknown
2917	18594594	Unknown
2918	18594767	Unknown
2919	18594954	Unknown
2920	18594992	Unknown
2921	18595043	Unknown
2922	18595057	Unknown
2923	18595318	Unknown
2924	18595340	Unknown
2925	18595665	Unknown
2926	18596319	glycerol kinase (H. sapiens) , similar to
2927	18596413	Unknown
2928	18596484	Unknown
2929	18596861	RAS-RELATED PROTEIN RAB-15 , similar to
2930	18597225	Unknown
2931	18597549	ZINC FINGER PROTEIN 268 (ZINC FINGER PROTEIN HZF3) , similar to
2932	18597551	Unknown
2933	18597742	Unknown
2934	18598132	Unknown
2935	18598291	kinesin family member C3
2936	18598462	Unknown
2937	18598482	Unknown

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2938	18598674	Unknown
2939	18598989	Unknown
2940	18599137	zinc finger protein 2 (A1-5)
2941	18599227	Unknown
2942	18599297	EphB1
2943	18599533	polyhomeotic 2 protein , similar to
2944	18599587	Unknown
2945	18600174	Unknown
2946	18600186	Unknown
2947	18600274	Unknown
2948	18600320	Unknown
2949	18600459	axonal transport of synaptic vesicles
2950	18600477	Unknown
2951	18600510	Unknown
2952	18600673	replication initiation region protein (60kD) (H. sapiens) , similar to
2953	18600792	Unknown
2954	18600878	Unknown
2955	18600890	Unknown
2956	18601250	Unknown
2957	18601419	Unknown
2958	18601439	Unknown
2959	18601460	Unknown
2960	18601629	huntingtin interacting protein-1-related (H. sapiens) , similar to
2961	18601927	Unknown
2962	18602066	Unknown
2963	18602347	Unknown
2964	18602382	chromosome condensation-related SMC-associated protein 1
2965	18602858	PUTATIVE NUCLEOSIDE DIPHOSPHATE KINASE (NDK) (NDP KINASE) , similar to
2966	18602966	Unknown
2967	18603033	Unknown
2968	18603423	Unknown
2969	18603588	solute carrier family 1 (glial high affinity glutamate transporter), member 2
2970	18603701	Unknown
2971	18603711	Unknown
2972	18603795	Unknown
2973	18603941	PHOSPHATIDYLINOSITOL 3-KINASE REGULATORY SUBUNIT (IB PI3-KINASE P101 SUBUNIT) (PTDINS-3-KINASE P101) (PI3K) (P101-PI3K) , similar to
2974	18604379	Unknown
2975	18604520	Unknown
2976	18604537	rab-related GTP-binding protein

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
2977	18604876	exostoses (multiple) 2 (H. sapiens) , similar to
2978	18605074	Unknown
2979	18605322	Unknown
2980	18605359	Unknown
2981	18606573	Unknown
2982	18645167	annexin A2
2983	18676544	Unknown
2984	18676570	Unknown
2985	18676847	Unknown
2986	18860829	optic atrophy 1, isoform 1
2987	18860843	optic atrophy 1, isoform 7
2988	18916767	Unknown
2989	18916841	Unknown
2990	18959202	leucine-rich PPR-motif containing; leucine-rich protein mRNA
2991	19115954	dynein, axonemal, heavy polypeptide 5
2992	19263915	Unknown
2993	19353103	Unknown
2994	19526647	oxidored-nitro domain-containing protein
2995	19584385	Unknown
2996	19684029	Unknown
2997	19743821	integrin beta 1 isoform 1C-2 precursor; integrin VLA-4 beta subunit; fibronectin receptor beta subunit
2998	19850567	breast carcinoma amplified sequence 3
2999	19923102	holocarboxylase synthetase (biotin-[proprionyl-Coenzyme A-carboxylase (ATP-hydrolysing)] ligase); Holocarbyoxylase synthetase; holocarboxylase synthetase
3000	19923233	sterol carrier protein 2
3001	19923611	Unknown
3002	19923717	rhysin 2
3003	19923721	pre-T-cell receptor alpha precursor
3004	19923757	golgi autoantigen, golgin subfamily a, 2; golgin-95
3005	20070212	voltage-dependent anion channel 3
3006	20070798	androgen-regulated short-chain dehydrogenase/reductase 1
3007	20127408	hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-Coenzyme A hydratase (trifunctional protein), alpha subunit; Hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/
3008	20127473	glucose regulated protein, 58kD
3009	20127510	peroxisomal long-chain acyl-coA thioesterase; peroxisomal long-chain acyl-coA thioesterase ; putative protein
3010	20140018	mitochondrial ribosomal protein S9, precursor (MRP-S9)
3011	20140250	Sideroflexin 1

SEQ ID NO:	GENBANK ACC. NO.	DESCRIPTION OF MITOCHONDRIAL PROTEINS
3012	20141424	Short chain 3-hydroxyacyl-CoA dehydrogenase, mitochondrial precursor (HCDH)
3013	20141538	Homeobox protein Hox-C12 (Hox-3F)
3014	20141568	Isocitrate dehydrogenase [NADP], mitochondrial precursor (Oxalosuccinate decarboxylase) (IDH) (NADP+-specific ICDH) (IDP) (ICD-M)
3015	20141580	Mitochondrial 2-oxoglutarate/malate carrier protein (OGCP)
3016	20141765	Succinyl-CoA ligase [GDP-forming] alpha-chain, mitochondrial precursor (Succinyl-CoA synthetase, alpha chain) (SCS-alpha)
3017	20141946	DNA topoisomerase II, beta isozyme
3018	20147036	transient receptor potential cation channel protein
3019	20150348	Deoxy Hbalphayq, A Mutant Of Hba
3020	20151189	Glutamate Dehydrogenase-Apo Form
3021	20178093	Suppressor of cytokine signaling 7 (SOCS-7) (Nck, Ash and phospholipase C gamma-binding protein) (Nck-associated protein 4) (NAP-4)
3022	20268814	CD36 antigen (collagen type I receptor, thrombospondin receptor)
3023	20270305	synaptotagmin-like 5
3024	20270399	polycystic kidney and hepatic disease 1
3025	226207	dihydrolipoamide S-acetyltransferase

Table 2 presents a selected subset of the 3025 human heart mitochondrial proteins that are disclosed in Table 1 and in the Sequence Listing. The mitochondrial proteins of Table 2 are organized according to particular mitochondrial function classifications as indicated, based on analysis of amino acid sequences and GENBANK annotations; a number of the entries in Table 2 may use earlier GENBANK Accession numbers which differ from those shown in Table 1, but the sequences of such GENBANK Accession numbers can each be matched to a sequence in the Sequence Listing of the instant application using sequence database searching software tools as exemplified above and as known to the art (*e.g.,* Basic Local Alignment Search Tool ("BLAST"), http://www.ncbi.nlm.nih.gov/BLAST, Altschul, *J. Mol. Biol. 219*:555-565, 1991, Henikoff et al., *Proc. Natl. Acad. Sci. USA 89*:10915-10919, 1992; PSI-BLAST, ALIGN, MEGALIGN; WISETOOLS. CLUSTAL W, Thompson et al., 1994 *Nucl. Ac. Res.* 22:4673; CAP, www.no.embnet. org/clustalw.html; FASTA/FASTP, Pearson, 1990 *Proc. Nat. Acad. Sci. USA* 85:2444, available from D. Hudson, Univ. of

Virginia, Charlottesville, VA). As described above, each amino acid sequence provides a polypeptide structure from which a sample can be analyzed to determine, on the basis of structure, whether a modified polypeptide as provided herein may be present in the sample. As also described above, each functional classification refers to a defined biological activity measureable according to methods provided herein and known to the art, such that the invention contemplates determination in a sample of whether a polypeptide that exhibits altered biological activity is present.

TABLE 2. MITOCHONDRIAL FUNCTIONS OF SELECTED COMPONENTS OF THE HUMAN HEART MITOCHONDRIAL PROTEOME

MITOCHONDRIAL FUNCTION CLASSIFICATION	GENBANK ACC NO.	SEQ ID NO:
Amino acid metabolism	118533	351
	2695812	563
	4504067	75
	4758714	527
	6624122	4
	11545863	520
	12653507	76
	13027640	491
	13518228	519
	14764412	240
	14775546	506
	16877964	453
Amino acid metabolism Total	**12**	
Apoptosis	2286145	159
	10437144	843
	10835173	637
	12382773	158
	14729475	101
	14761496	717
	16163817	100
Apoptosis Total	**7**	
C-compound metabolism	1354222	40
	4758498	405

MITOCHONDRIAL FUNCTION CLASSIFICATION	GENBANK ACC NO.	SEQ ID NO:
	11275986	360
	11428230	37
	11436533	36
	12230075	359
	12652981	361
	13630862	39
	14043187	38
	14724751	695
C-compound metabolism Total	**10**	
Carrier	113463	153
	4505775	157
	4557403	155
	7657347	532
	11141885	851
	12232421	920
	12653827	531
	13632616	152
	13647558	151
	14747216	154
	14752024	850
	14774525	156
Carrier Total	**12**	
Complex 1	13013	599
	1262579	583
	1262580	592
	4505355	620
	4505357	609
	4505359	613
	4505361	611
	4505365	617
	4505367	605
	4689104	610
	4758768	600
	4758772	621
	4758776	607
	4758784	614
	4758786	601
	4758790	588
	4758792	586

MITOCHONDRIAL FUNCTION CLASSIFICATION	GENBANK ACC NO.	SEQ ID NO:
	4826848	612
	4826852	608
	4894370	619
	6041669	616
	7657369	591
	10092657	585
	10179599	622
	10764847	618
	10835025	596
	10835087	584
	12005918	369
	13097156	598
	13272567	602
	13272568	604
	13528960	590
	13637608	606
	14336775	623
	14769051	615
	14777313	587
	15307634	595
Complex 1 Total	**37**	
Complex 2	4759080	865
	13639114	792
	14727486	867
	16157047	791
Complex 2 Total	**4**	
Complex 3	117759	944
	117863	947
	190804	946
	1351360	934
	9297078	933
	11128019	233
	13631678	945
	13649658	948
	14736223	942
	14775827	943
Complex 3 Total	**10**	
Complex 4	117103	211
	226209	221

MITOCHONDRIAL FUNCTION CLASSIFICATION	GENBANK ACC NO.	SEQ ID NO:
	1262581	207
	4502985	213
	4502987	218
	4502989	217
	4502991	219
	4502993	220
	4758038	210
	4758040	215
	13629150	209
	13637833	216
	13648426	237
	16196598	212
Complex 4 Total	**14**	
Complex 5	114549	84
	1262582	80
	4502297	87
	4502303	93
	5901896	89
	6005717	88
	11526149	85
	13272855	81
	13543618	83
	14774139	91
Complex 5 Total	**10**	
DNA synthesis	118749	497
	1709123	281
	4153874	840
	11225260	283
DNA synthesis Total	**4**	
Glycolysis	31645	355
	107554	752
	129070	750
	136066	921
	387011	751
	4557032	467
	11430299	401
	12653371	684
	13436413	350
	14043654	831

MITOCHONDRIAL FUNCTION CLASSIFICATION	GENBANK ACC NO.	SEQ ID NO:
	14761208	356
	15553127	403
	15991827	402
Glycolysis Total	**13**	
Guanine-related	106185	372
	121009	379
	386745	380
	1335250	784
	4504049	378
	4506517	764
	6005772	747
	10047118	344
	10945428	516
	11055998	376
	14745808	377
	15779126	375
	16181084	343
Guanine-related Total	**13**	
Inositol-related	108480	688
	124505	433
	1399105	682
	4505801	686
	10835023	431
	11436778	435
	14724557	683
	14728229	687
	14760649	432
	14783738	434
Inositol-related Total	**10**	
Kinase/phosphatase	130749	45
	1103677	573
	1709242	650
	4503269	246
	4505153	510
	4506091	551
	4557769	522
	7439346	737
	10047120	437
	11526789	430

MITOCHONDRIAL FUNCTION CLASSIFICATION	GENBANK ACC NO.	SEQ ID NO:
	12643716	738
	12654407	574
	12659007	733
	12830367	803
	13606056	280
	13631907	553
	13646385	222
	13648611	802
	13938619	224
	14194461	11
	14721507	801
	14733904	799
	14736227	774
	14740371	12
	14749765	10
	14782921	732
	14784064	552
	14785405	706
	15301488	418
	16033591	808
Kinase/phosphatase Total	**30**	
Lipid metabolism	1082723	722
	1169204	286
	1762533	148
	3273228	18
	4501869	22
	4502327	97
	4503607	295
	4503609	296
	4503651	322
	4504975	484
	4557817	869
	4557833	724
	4758312	297
	10835059	319
	11276083	323
	11433007	678
	11640566	421
	12669909	483

MITOCHONDRIAL FUNCTION CLASSIFICATION	GENBANK ACC NO.	SEQ ID NO:
	12707570	304
	12805021	19
	13435350	327
	13639628	13
	13647276	465
	13653049	20
	14041699	310
	14043451	373
	14725848	21
	14729783	252
	14730775	420
	14746487	815
	14764159	14
	14764202	419
	14769776	674
	14781245	324
Lipid metabolism Total	**34**	
Lipoprotein	229479	480
	1082692	693
	4826914	691
	9438229	692
	13470094	70
	14721241	485
Lipoprotein Total	**6**	
Nucleotide metabolism	4502013	28
	4502457	78
	4503375	258
	8671846	204
	13654685	79
	14776778	77
Nucleotide metabolism Total	**6**	
Protease	4502201	30
	4502563	137
	7656959	139
	10047106	144
	12408656	136
	12643637	24
	12654627	517
	14772672	138

MITOCHONDRIAL FUNCTION CLASSIFICATION	GENBANK ACC NO.	SEQ ID NO:
	14780055	727
	16741033	726
Protease Total	**10**	
Protein targeting	123571	385
	1091688	390
	1346317	387
	4008131	184
	5032181	915
	5802970	33
	6912714	916
	7657257	917
	7662673	918
	9910382	533
	12655195	391
	13645492	389
	14603309	386
Protein targeting Total	**13**	
ras/GTPase	1657266	789
	5803135	755
	11359874	371
	11436135	761
	12652715	648
	12751117	704
	13569962	845
	13651229	772
	13652324	760
	13786129	417
	13794267	757
	14211570	202
	14249144	754
	14740792	1390
ras/GTPase Total	**14**	
Receptor	184477	771
	1001941	257
	1168781	316
	4504733	436
	4877291	763
	11968152	852
	13632266	894

MITOCHONDRIAL FUNCTION CLASSIFICATION	GENBANK ACC NO.	SEQ ID NO:
	13650874	748
	14732886	895
	14744234	646
	16161569	788
Receptor Total	**11**	
Redox	802150	662
	4502601	143
	4557845	775
	6912536	633
	11399466	239
	11416669	632
	12804319	142
	13112023	199
	13236495	753
	13529257	41
	13627233	42
	13994325	744
	14735899	235
Redox Total	**13**	
Stress	4503731	331
	4758192	800
	5453902	634
	7643782	383
	13631440	675
	14250063	676
	14755436	874
Stress Total	**7**	
Structural	13194197	459
	13643253	460
	14124976	461
	14730782	462
	15305472	924
Structural Total	**5**	
TCA cycle	417178	450
	1071834	256
	1170477	451
	1718502	16
	5031777	448
	5174539	500

MITOCHONDRIAL FUNCTION CLASSIFICATION	GENBANK ACC NO.	SEQ ID NO:
	11321581	872
	11321583	868
	11374664	452
	12804901	449
	13627252	658
	13639817	505
	14740547	342
	14782063	501
	15318843	17
	16192638	446
TCA cycle Total	**16**	
Transcription	105294	48
	107912	905
	1033182	1400
	1582692	888
	2565032	904
	4506445	780
	4507389	301
	6678455	908
	6912440	287
	9884738	67
	11096171	783
	11761696	119
	11890755	782
	12653775	394
	12734816	741
	13242069	647
	13787197	242
	13938539	232
	14730158	889
	14742266	781
	14748858	910
	14766373	765
	14790190	847
	15296351	859
	15300149	558
	15451854	530
	16163124	926
Transcription Total	**27**	

MITOCHONDRIAL FUNCTION CLASSIFICATION	GENBANK ACC NO.	SEQ ID NO:
Translation	1706611	300
	4503507	311
	4758118	243
	5032051	6
	7661872	474
	7705626	543
	7706349	546
	11177148	535
	11416393	538
	11424404	544
	11559927	542
	11596859	537
	13027604	547
	13123976	73
	13559404	534
	13631521	549
	13648964	35
	13899231	541
	14028389	539
	14028405	545
	14165270	536
	14285174	299
	15150811	548
	15295574	469
	15298022	540
Translation Total	**25**	
Transport	28714	52
	114374	579
	1172554	1394
	1359715	578
	1588292	130
	4503057	225
	5729937	518
	5730033	848
	7799988	470
	8923870	408
	10716563	135
	10835220	94
	11612670	690

MITOCHONDRIAL FUNCTION CLASSIFICATION	GENBANK ACC NO.	SEQ ID NO:
	12803281	1395
	13376991	1396
	13540606	875
	13649217	1393
	14149607	186
	14739472	710
	14767738	134
	14778381	294
	16974753	849
Transport Total	**22**	
Tumor-related	120749	498
	132164	768
	1177438	123
	4507643	930
	10567164	348
	10835155	928
	10863907	397
	12246901	929
	12643796	770
	13529047	912
	13650639	515
	14725399	898
	14755336	931
	15076827	665
	15296762	1388
	16160929	769
Tumor-related Total	**16**	
Zinc finger	1177230	1401
	2117022	1402
	2317769	714
	3021386	1403
	4507979	1404
	4827065	1405
	5454180	1407
	7671629	464
	14211907	1410
	14286186	1406
	14670360	1409
	14755316	3025

MITOCHONDRIAL FUNCTION CLASSIFICATION	GENBANK ACC NO.	SEQ ID NO:
	14755456	1408
Zinc finger Total	**13**	

EXAMPLE 4

OXIDATIVE POST-TRANSLATIONAL MODIFICATION OF TRYPTOPHAN RESIDUES IN CARDIAC MITOCHONDRIAL PROTEINS

This example shows the distribution of N-formylkynurenine, a product of the dioxidation of tryptophan residues in proteins, throughout the human heart mitochondrial proteome. This oxidized amino acid was associated with a distinct subset of proteins, including an over-representation of complex I subunits as well as complex V subunits and enzymes involved in redox metabolism. No relationship was observed between the tryptophan modification and methionine oxidation, a known artifact of sample handling. As the mitochondria were isolated from normal human heart tissue and not subject to any artificially induced oxidative stress, the susceptible tryptophan residues in this group of proteins appeared, according to non-limiting theory, to be "hot spots" for oxidation in close proximity to a source of reactive oxygen species (ROS) in respiring mitochondria.

LC/MS/MS data generated from the human heart mitochondrial proteome project as described in the preceding Examples, as well as data for human and bovine proteins prepared by sucrose density gradient centrifugation as described above, or by immunoprecipitation using antibodies against complex V (ATP synthase) and/or complex I (NADH dehydrogenase) proteins (see, Table 2), were queried against the human or bovine subsets of GenBank using the Sonar MSMS searching algorithm (Genomic Solutions, Ann Arbor, MI) with oxidation of methionine (+16 u) and tryptophan (+32 u) specified as differential modifications. Corresponding MALDI spectra were manually inspected. Figure 3 shows oxidation products of tryptophan from proteins, including N-formylkynurenine (Structure 2).

Modifications to complex I subunits in bovine heart mitochondria in response to the oxidative stress caused by peroxynitrite treatment were studied *in*

vitro, and yielded evidence of oxidized tryptophan in several subunits, both by MALDI TOF and by LC/MS/MS. Surprisingly, the relative intensities of the peaks in the MALDI spectra corresponding to peptides containing N-formylkynurenine were also high in untreated mitochondria from some bovine and human heart preparations, although there was substantial variation. Prior to complex I isolation and electrophoresis, mitochondria were prepared identically from all hearts which were freshly collected, frozen and thawed immediately prior to analysis. Figure 4 shows the MALDI spectra of peptides from the human complex I subunit, NDUFS4 (see Table 3), and its bovine homologue from five different preparations corresponding to seven different hearts (five human, including one pooled sample of mitochondria from three individual hearts, and two bovine hearts). The relative intensities of m/z 1329.6 and 1361.6 (corresponding to peptides without and with dioxidized tryptophan, Fig. 4A) and 1112.5 and 1128.5 (corresponding to peptides without and with oxidized methionine, Fig. 4B) were used as a rough measure of protein oxidation. No correlation was found between the extent of tryptophan oxidation and that of methionine oxidation, suggesting that they occurred via different mechanisms.

The dioxidation of tryptophan was clearly discernable in Fig. 4A (i) and (ii) in which complex I was purified by different methods, sucrose density gradient centrifugation or immunoprecipitation, respectively, but corresponded to mitochondria from the same human heart. This finding suggested that the method of preparation was not a factor in determining the extent of oxidation, but rather that such oxidation was a characteristic of the donor from which the sample was obtained (in this case, a 41-year-old male Caucasian who died of brain cancer). The other human donor, displaying far less extensive oxidation of tryptophan as seen in Fig. 4A (iii), was a 62-year-old female Caucasian who died of intracranial bleeding. In contrast, NDUFS4 from a pool of mitochondria from three human hearts displayed an extensively oxidized tryptophan-containing peptide Fig. 4A (iv). Again the degree of oxidation in the pooled sample was not commensurate with the degree of oxidation for the methionine-containing fragment Fig. 4B (iv).

Distribution of the oxidatively modified tryptophan in the MS/MS spectra dataset described in the preceding Examples was assessed by reanalyzing the data with N-formylkynurenine selected as a differential modification of tryptophan (+32) using the SonarMSMS algorithm according to the supplier's instructions (Genomic Solutions, Ann Arbor, MI). Table 3 lists N-formylkynurenine-containing peptides found with peptide expect scores (Epep) values $\leq 1 \times 10^{-2}$ (99% confidence); also listed in Table 3 are the identifiers for the mitochondrial polypeptide sequences from which these peptides derived. Of this list of 51 peptide sequences from 39 proteins, 9 subunits of complex I had N-formylkyenurine-containing tryptic peptides and included two newly discovered subunits (Table 1, NCBI/ Genbank Acc. Nos. 13938442 and 17455445, now 21754001). This subset of proteins was used to compare tryptophan oxidation versus methionine oxidation as a function of the ability to observe a peptide in any given LC/MS/MS experiment. As shown in Fig. 5, the numbers of distinct peptides containing methionine (A) and tryptophan (B) were plotted for a given complex I subunit which had a Sonar MSMS Epep score of $\leq 1 \times 10^{-2}$, and on each plot Figure 5 indicates whether the corresponding oxidized residue was observed. Methionine oxidation appeared to be directly related to the number of observable peptides that would be expected if oxidation were a random sample-handling artifact. In contrast, tryptophan oxidation appeared to be much more specific to selected subunits, with the greatest modification being noted for NDUFV1 (51 kDa flavoprotein 1) and NDUFA9 (a 39 kDa reductase/isomerase subunit). In addition, five subunits of the iron-protein component were oxidized.

TABLE 3

PEPTIDES CONTAINING DOUBLY OXIDIZED TRYPTOPHAN FROM THE CARDIAC MITOCHONDRIAL PROTEOME.

PEPTIDE	Epep	Peptide Derived from NCBI/ Genbank Acc. No.	PROTEIN DESCRIPTION
VFEISPFEPwITR	1.40E-05	6681764	NDUFA9
FGPIPLGSLGwK	2.30E-04	6681764	NDUFA9
wLSAEIEDVKPAK	1.80E-03	6681764	NDUFA9
HAGGVTGGwDNLLAVIPGGSSTPLIPK	2.10E-04	20149568	NDUFV1
GDARPAEIDSLwEISK	9.40E-04	20149568	NDUFV1
GPDwILGEIK	2.40E-03	20149568	NDUFV1
LAALPENPPAIDwAYYK	3.20E-05	5453559	ATPase d F0
TIDwVAFAEIIPQNQK	2.10E-03	5453559	ATPase d F0
YPYwPHQPIENL	7.20E-03	5453559	ATPase d F0
wVVIGDENYGEGSSR	8.40E-08	3600098	aconitase precursor
VAEKEGwPLDIR	4.00E-04	3600098	aconitase precursor
LwISNGGLADIFTVFAK	2.90E-06	18044943	acyl-Coenzyme A dehydrogenase, very long chain
IFGSEAAwK	3.90E-03	18044943	acyl-Coenzyme A dehydrogenase, very long chain
ALGVLAQLIwSR	1.10E-05	4758076	citrate synthase precursor
DYIwNTLNSGR	7.10E-04	4758076	citrate synthase precursor
KLETAVNLAwTAGNSNTR	1.60E-05	4507879	VDAC-1
wNTDNTLGTEITVEDQLAR	5.30E-03	4507879	VDAC-1
VVDGAVGAQwLAEFR	4.70E-05	17458911	dihydrolipoamide S-acetyltransferase
VPEANSSwMDTVIR	6.60E-04	17458911	dihydrolipoamide S-acetyltransferase
SAVTALwGK	3.70E-03	4504349	beta globin
LLVVYPwTQR	4.30E-03	4504349	beta-globin
RPPEPTTPwQEDPEPEDENLYEK	6.80E-08	13938442	neuronal protein (ND17.3)
NLTQYSwLLDGFPR	1.00E-06	19923437	adenylate kinase 3 alpha like

PEPTIDE	Epep	Peptide Derived from NCBI/ Genbank Acc. No.	PROTEIN DESCRIPTION
FDLNSPwEAFPVYR	2.10E-05	11360206	NDUFS3
IASGLGLAwIVGR	2.60E-05	4758714	microsomal glutathione S-transferase 3
GYIVIEDLwK	2.90E-05	12001992	brain my025
ASSTSPVEISEwLDQK	4.00E-05	4503607	electron transfer flavoprotein alpha polypeptide
GRPTSTNPIASIFAwTR	6.40E-05	4504575	isocitrate dehydrogenase 2 (NADP+), mitochondrial
GLLTYTSwEDALSR	1.40E-04	21411235	NDUFS1
IPwFQYPIIYDIR	1.90E-04	6005854	D-prohibitin
GLSDGEwQLVLNVwGK	2.50E-04	229361	Myoglobin
ASwSSLSMDEK	3.00E-04	5921895	Cytochrome c oxidase subunit IV isoform 1
LDDLVNwAR	5.30E-04	21750696	NDUFS7
TLLwTELFR	7.80E-04	4505371	NDUFS8
SYGANFSwNK	8.70E-04	13528960	NDUFS4
ASLHALVGSPIIwGGEPR	9.90E-04	13676336	long-chain acyl-coA thioesterase peroxisomal
wEVADLQPQLK	1.20E-03	21903482	Ubiquinol-cytochrome C reductase complex core protein 2
YEGFFSLwK	1.30E-03	21361114	mitochondrial carrier; oxoglutarate carrier
LITTQQwLIK	1.40E-03	13272660	ATP synthase 6
LWEPLVEEPPADQwK	1.50E-03	4826848	NDUFA5
IDEAILITwTK	2.00E-03	15991833	hexokinase 1
wDGQETTLVR	3.30E-03	458862	fatty acid binding protein, heart ; hFABP
HwLDSPwPGFFTLDGQPR	3.40E-03	20541592	2-oxoglutarate dehydrogenase E1 component, mitochondrial precursor
AwNGSAEGPGKVER	4.30E-03	21754001	Unnamed protein product (NDUFB11)
ELwFSDDPNVTK	4.70E-03	4757732	programmed cell death 8 (apoptosis-inducing

PEPTIDE	Epep	Peptide Derived from NCBI/ Genbank Acc. No.	PROTEIN DESCRIPTION
			factor AIF)
EQwDTIEELIR	5.30E-03	4503301	2,4-dienoyl CoA reductase 1 precursor
GAwSNVLR	5.30E-03	86754	carrier ANT
wYYNAAGFNK	5.30E-03	5454152	UCR ubiquinone-binding protein (VI)
ELDSITPEVLPGwK	5.50E-03	8131894	Mitofilin
APLAEEwDNMTMK	8.10E-03	4505093	monoamine oxidase B
LATFwYYAK	9.10E-03	22096328	ATP synthase G chain, mitochondrial

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

What is claimed is:

1. A method for identifying a mitochondrial target for therapeutic intervention in treatment of a disease associated with altered mitochondrial function, comprising:

(a) determining a presence, in a biological sample from a subject known to have or suspected of having a disease associated with altered mitochondrial function, of at least one modified polypeptide, said modified polypeptide comprising at least one modification to a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1- 3025; and

(b) correlating the modification with at least one disease associated with altered mitochondrial function, and therefrom identifying a mitochondrial target for therapeutic intervention.

2. The method of claim 1 wherein the modified polypeptide exhibits altered biological activity.

3. The method of claim 1 wherein the biological sample is selected from the group consisting of blood, skin, skeletal muscle, liver and cartilage.

4. The method of claim 1 wherein the disease associated with altered mitochondrial function is selected from the group consisting of Alzheimer's disease, diabetes mellitus, Parkinson's disease, Huntington's disease, osteoarthritis, dystonia, Leber's hereditary optic neuropathy (LHON), mitochondrial encephalopathy, lactic acidosis, and stroke (MELAS), myoclonic epilepsy ragged red fiber syndrome (MERRF) and cancer.

5. The method of claim 1 wherein the modification is selected from the group consisting of an amino acid substitution, an amino acid insertion, an amino acid deletion, a posttranslational modification and an altered expression level.

6. The method of claim 4 wherein the posttranslational modification is selected from the group consisting of glycosylation, phosphorylation, nitration, nitrosylation, amidation, fatty acylation and oxidative modification.

7. A method of identifying an agent for treating a disease associated with altered mitochondrial function, comprising:

(a) contacting a candidate agent with a biological sample from a subject having a disease associated with altered mitochondrial function, wherein said sample comprises at least one polypeptide that exhibits altered biological activity which accompanies said disease and wherein the polypeptide is selected from the group consisting of (i) a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1- 3025 and (ii) a modified polypeptide that comprises at least one modification to a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1- 3025; and

(b) determining an increase or decrease in the altered biological activity of the polypeptide in the presence of the candidate agent relative to the level of the altered biological activity in the absence of the candidate agent, and therefrom identifying an agent for treating a disease associated with altered mitochondrial function.

8. The method of claim 7 wherein the altered biological activity is an indicator of altered mitochondrial function that is selected from the group consisting of ATP biosynthesis, oxidative phosphorylation, calcium uptake, calcium release, maintenance of inner mitochondrial membrane potential, mitochondrial

permeability transition, ETC-mediated electron transport and intermembrane space protein release.

9. The method of claim 7 wherein the sample is selected from the group consisting of a cell, a mitochondria enriched sample, an isolated mitochondrion and a submitochondrial particle.

10. The method of claim 7 wherein the disease associated with altered mitochondrial function is selected from the group consisting of Alzheimer's disease, diabetes mellitus, Parkinson's disease, Huntington's disease, osteoarthritis, dystonia, Leber's hereditary optic neuropathy (LHON), mitochondrial encephalopathy, lactic acidosis, and stroke (MELAS), myoclonic epilepsy ragged red fiber syndrome (MERRF), and cancer.

11. A method of treating a disease associated with altered mitochondrial function comprising administering to a subject in need thereof an agent that compensates for at least one biological activity of a polypeptide that exhibits altered biological activity which accompanies said disease, wherein the polypeptide is selected from the group consisting of (i) a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1- 3025 and (ii) a modified polypeptide that comprises at least one modification to a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1- 3025.

12. A method for identifying a risk for having or a presence of a disease associated with altered mitochondrial function, comprising:

(a) determining a presence, in a biological sample from a subject suspected of having a disease associated with altered mitochondrial function, of at least one modified polypeptide, said modified polypeptide comprising at least one modification to a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1- 3025, wherein the modification

correlates with at least one disease associated with altered mitochondrial function, and therefrom identifying a risk for or presence of disease.

13. A method of identifying an agent for treating a disease associated with altered mitochondrial function, comprising:

(a) contacting a candidate agent with an isolated polypeptide that exhibits altered biological activity which accompanies a disease associated with altered mitochondrial function, wherein the polypeptide is selected from the group consisting of (i) a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1-3025 and (ii) a modified polypeptide that comprises at least one modification to a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1-3025; and

(b) determining an increase or decrease in the altered biological activity of the polypeptide in the presence of the candidate agent relative to the level of the altered biological activity in the absence of the candidate agent, and therefrom identifying an agent for treating a disease associated with altered mitochondrial function.

14. The method of claim 13 wherein the disease associated with altered mitochondrial function is selected from the group consisting of Alzheimer's disease, diabetes mellitus, Parkinson's disease, Huntington's disease, osteoarthritis, dystonia, Leber's hereditary optic neuropathy (LHON), mitochondrial encephalopathy, lactic acidosis, and stroke (MELAS), myoclonic epilepsy ragged red fiber syndrome (MERRF), and cancer.

15. The method of claim 13 wherein the isolated polypeptide is present in a preparation that is selected from the group consisting of a submitochondrial particle, a proteoliposome and a mitochondrial protein fraction.

16. A method of identifying an agent for treating a disease associated with altered mitochondrial function, comprising:

(a) administering a candidate agent to a subject having a disease associated with altered mitochondrial function; and

(b) determining, in a first biological sample obtained from the subject prior to the step of administering the candidate agent and in a second biological sample obtained from the subject subsequent to the step of administering the candidate agent, wherein each of said first and second samples comprises at least one polypeptide that exhibits altered biological activity which accompanies said disease and wherein the polypeptide is selected from the group consisting of (i) a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1-3025 and (ii) a modified polypeptide that comprises at least one modification to a polypeptide having an amino acid sequence as set forth in any one of SEQ ID NOS 1-3025,

an increase or decrease in the altered biological activity of the polypeptide in the second sample relative to the level of the altered biological activity in the first sample, and therefrom identifying an agent for treating a disease associated with altered mitochondrial function.

17. The method of claim 16 wherein the altered biological activity is an indicator of altered mitochondrial function that is selected from the group consisting of ATP biosynthesis, oxidative phosphorylation, calcium uptake, calcium release, maintenance of inner mitochondrial membrane potential, mitochondrial permeability transition, ETC-mediated electron transport and intermembrane space protein release.

18. The method of claim 16 wherein the sample is selected from the group consisting of a cell, a mitochondria enriched sample, an isolated mitochondrion and a submitochondrial particle.

19. The method of claim 16 wherein the disease associated with altered mitochondrial function is selected from the group consisting of Alzheimer's disease, diabetes mellitus, Parkinson's disease, Huntington's disease,

osteoarthritis, dystonia, Leber's hereditary optic neuropathy (LHON), mitochondrial encephalopathy, lactic acidosis, and stroke (MELAS), myoclonic epilepsy ragged red fiber syndrome (MERRF), and cancer.

FIGURE 1

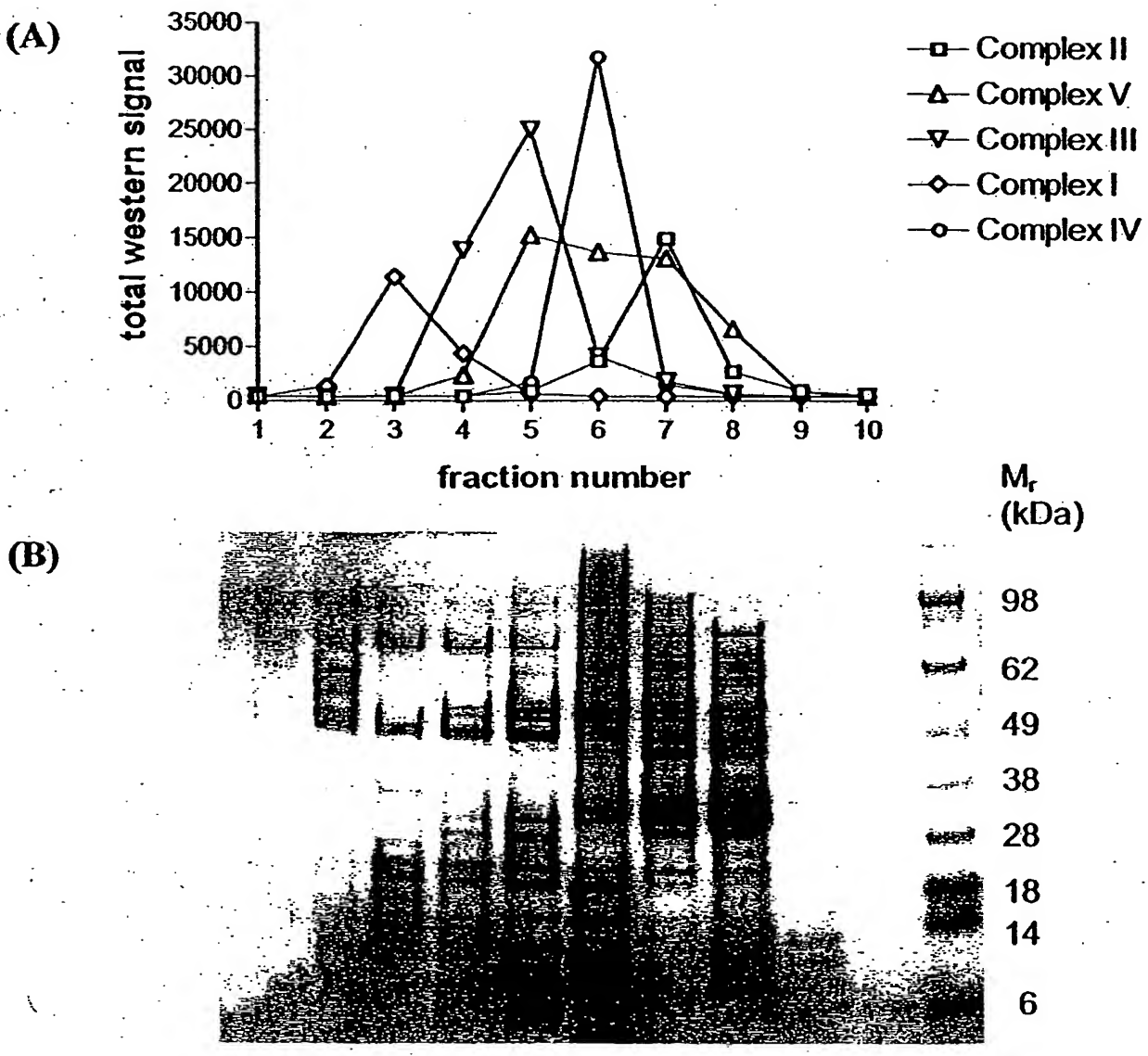
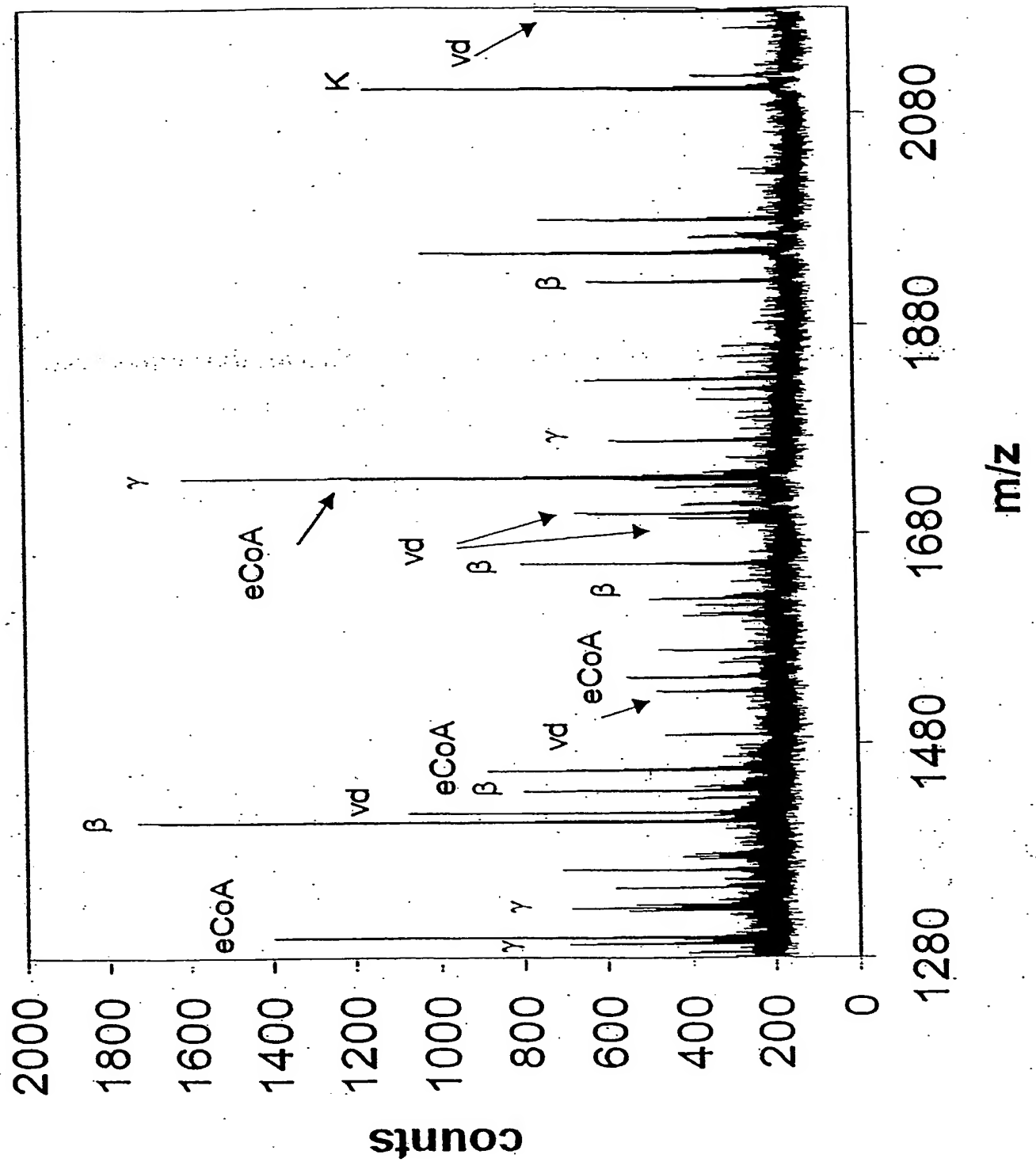

(A)
total western signal
35000
30000
25000
20000
15000
10000
5000
0
1
2
3
4
5
6
7
8
9
10
fraction number
Complex II
Complex V
Complex III
Complex I
Complex IV
(B)
M_r (kDa)
98
62
49
38
28
18
14
6

FIGURE 2


counts
m/z
2000
1800
1600
1400
1200
1000
800
600
400
200
0
1280
1480
1680
1880
2080
eCoA
β
vd
γ
K

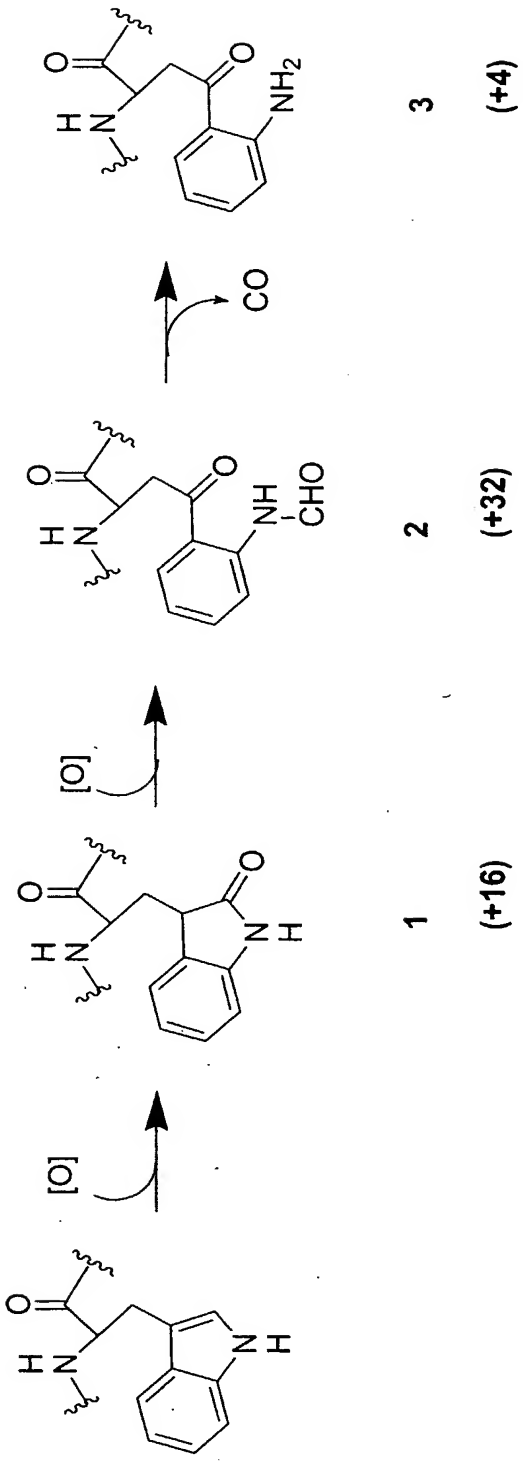


Figure 3

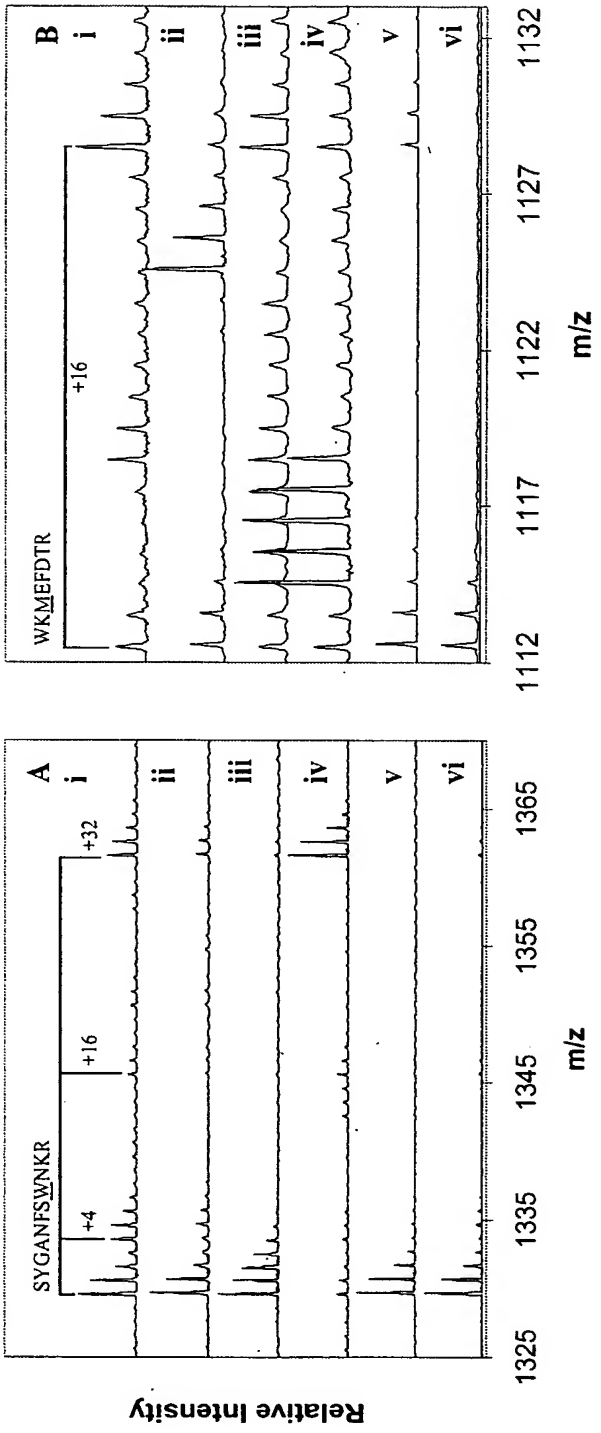
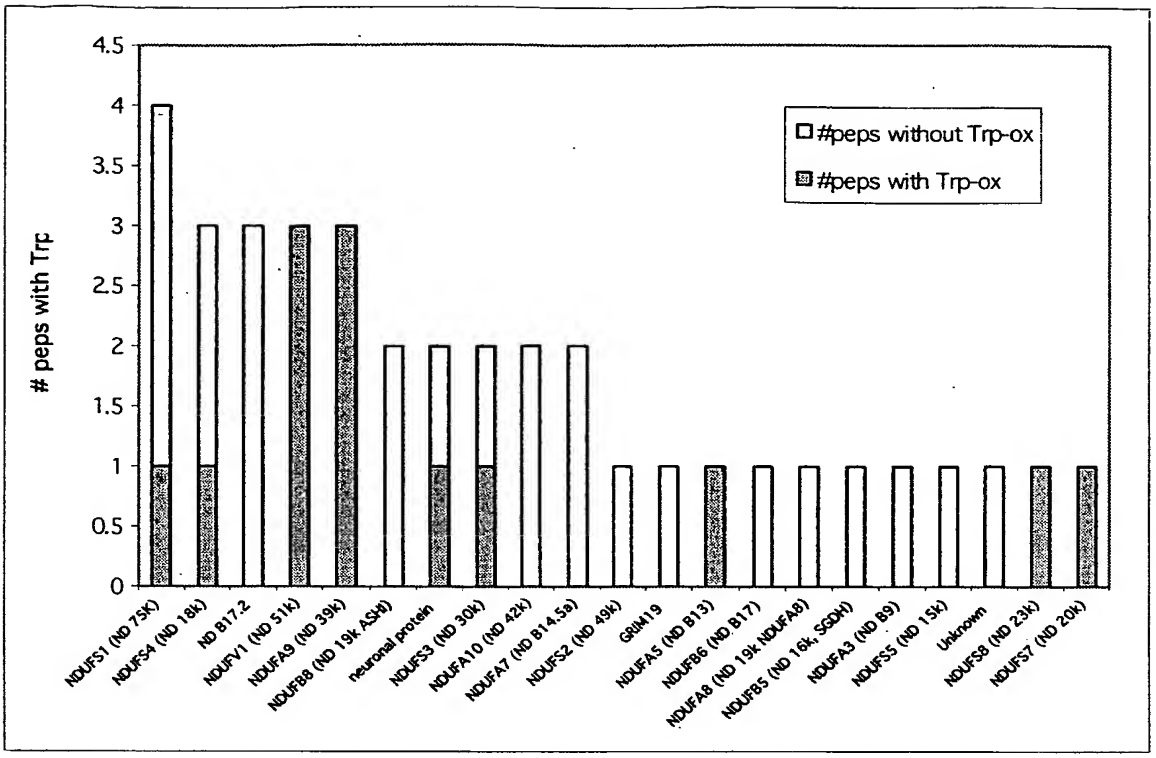


Figure 4 Taylor et al.



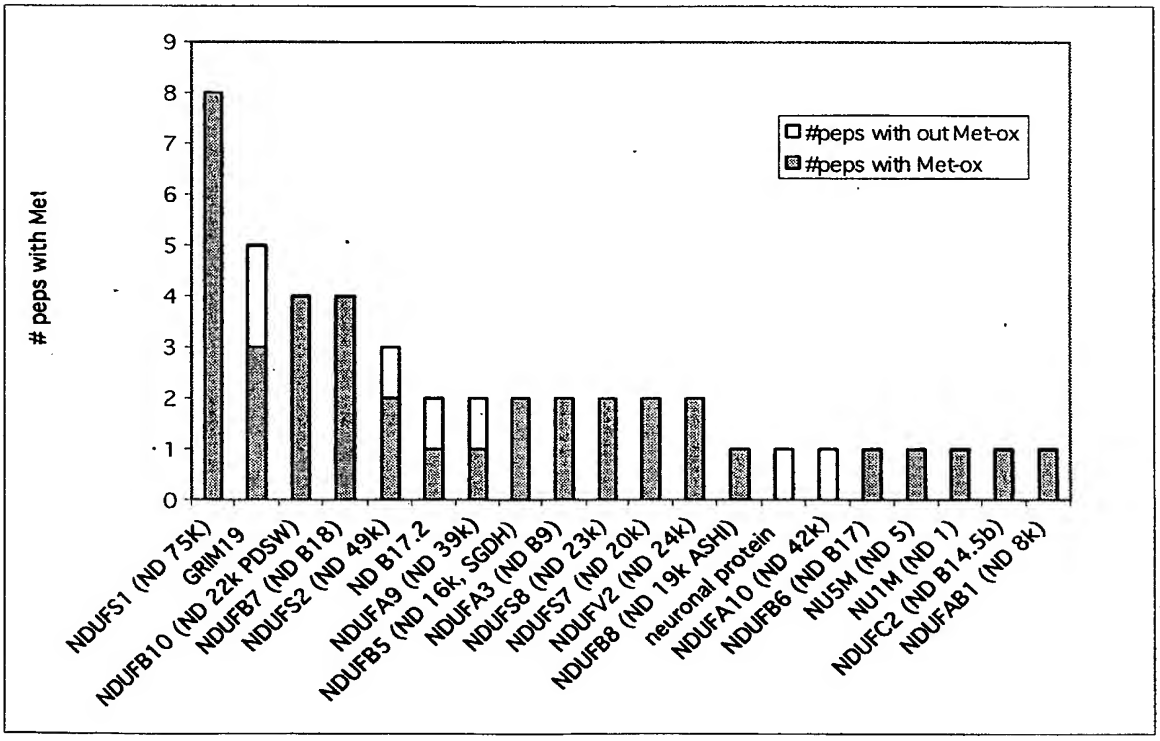


Figure 5

Taylor et al.